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(21) International Application Number: PCT/US98/12668 (22) International Filing Date: 17 June 1998 (17.06.98) (30) Priority Data: 08/877,846 18 June 1997 (18.06.97) US (71) Applicant: SYNAPTIC PHARMACEUTICAL CORPORATION [US/US]; 215 College Road, Paramus, NJ 07652 (US). (72) Inventors: LAGU, Bharat; 94 East Pleasant Avenue, Maywood, NJ 07607 (US). DHAR, T., G., Murali; 32 East Periwinkle Lane, Hitchens Farm, Newark, DE 19711 (US). NAGARATHNAM, Dhanapalan; Apartment 74, 450 Island Avenue, Ramsey, NJ 07446 (US). JEON, Yoon, T.; 411 Ponfield Place, Ridgewood, NJ 07450 (US). MARZABADI, Mohammad, R.; 153 Woodland Avenue, Ridgewood, NJ 07450 (US). WONG, Wai, C.; 34 Columbia Street, Newark, NJ 07102 (US). GLUCHOWSKI, Charles; 154 Coolspring Court, Danville, CA 94506 (US). TIAN, Dake; 24-10 Quail Ridge Drive, Plainsboro, NJ 08536 (US). (74) Agent: WHITE, John, P.; Cooper & Dunham LLP, 1185 Avenue of the Americas, New York, NY 10036 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: HETEROCYCLIC SUBSTITUTED PIPERIDINES AND USES THEREOF (57) Abstract This invention is directed to oxazolidinone compounds which are selective antagonists for human α_{1A} receptors. This invention is also related to uses of these compounds for lowering intraocular pressure, inhibiting cholesterol synthesis, relaxing lower urinary tract tissue, the treatment of benign prostatic hyperplasia, impotency, cardiac arrhythmia and for the treatment of any disease where the antagonism of the α_{1A} receptor may be useful. The invention further provides a pharmaceutical composition comprising a therapeutically effective amount of the above-defined compounds and a pharmaceutically acceptable carrier.		

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HETEROCYCLIC SUBSTITUTED PIPERIDINES AND USES THEREOF

Throughout this application, various references are referred to within parentheses. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

Background of the Invention

The designation " α_{1A} " is the appellation recently approved by the IUPHAR Nomenclature Committee for the previously designated " α_{1c} " cloned subtype as outlined in the 1995 Receptor and Ion Channel Nomenclature Supplement (Watson and Girdlestone, 1995). The designation α_{1A} is used throughout this application and the supporting tables and figures to refer to this receptor subtype. At the same time, the receptor formerly designated α_{1A} was renamed α_{1D} . The new nomenclature is used throughout this application. Stable cell lines expressing these receptors are described herein; however, these cell lines were deposited with the American Type Culture Collection (ATCC) under the old nomenclature (*infra*).

Benign Prostatic Hyperplasia (BPH), also called Benign Prostatic Hypertrophy, is a progressive condition which is characterized by a nodular enlargement of prostatic tissue resulting in obstruction of the urethra. This results in increased frequency of urination, nocturia, a poor urine stream and hesitancy or delay in starting the urine flow. Chronic consequences of BPH can include hypertrophy of bladder smooth muscle, a decompensated

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bladder and an increased incidence of urinary tract infection. The specific biochemical, histological and pharmacological properties of the prostate adenoma leading to the bladder outlet obstruction are not yet
5 known. However, the development of BPH is considered to be an inescapable phenomenon for the aging male population. BPH is observed in approximately 70% of males over the age of 70. Currently, in the United States, the method of choice for treating BPH is surgery
10 (Lepor, H., Urol. Clinics North Amer., 17, 651 (1990)). Over 400,000 prostatectomies are performed annually (data from 1986).

Transurethral resection of the prostate (TURP) was used
15 in approximately 180,000 men in the United States in 1996. This surgical procedure results in significant benefit. However, because of its potential adverse consequences, surgery is an unattractive alternative for many patients and is not recommended for elderly
20 patients due to the potential for complications. Another surgical procedure, transurethral needle ablation (TUNA), was recently approved by the FDA and may have the advantage of possible use on an out-patient basis under local anesthesia. However, initial results
25 of a recent study comparing TURP and TUNA show a lower level of efficacy in TUNA than in TURP with respect to increasing urinary flow.

A medicinal alternative to surgery is clearly very
30 desirable. The limitations of surgery for treating BPH include the morbidity rate of an operative procedure in elderly men, persistence or recurrence of obstructive and irritative symptoms, as well as the significant cost of surgery.

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α -Adrenergic receptors (McGrath, et. al. Med. Res. Rev., 9, 407-533, 1989) are specific neuroreceptor proteins located in the peripheral and central nervous systems on tissues and organs throughout the body. These receptors are important switches for controlling many physiological functions and, thus, represent important targets for drug development. In fact, many α -adrenergic drugs have been developed over the past 40 years. Examples include clonidine, phenoxybenzamine and prazosin (treatment of hypertension), naphazoline (nasal decongestant), and apraclonidine (treating glaucoma). α -Adrenergic drugs can be broken down into two distinct classes: agonists (clonidine and naphazoline are agonists), which mimic the receptor activation properties of the endogenous neurotransmitter norepinephrine, and antagonists (phenoxybenzamine and prazosin are antagonists), which act to block the effects of norepinephrine. Many of these drugs are effective but also produce unwanted side effects (for example, clonidine produces dry mouth and sedation in addition to its antihypertensive effects).

During the past 15 years a more precise understanding of α -adrenergic receptors and their drugs has evolved through increased scientific scrutiny. Prior to 1977, only one α -adrenergic receptor was known to exist. Between 1977 and 1988, it was accepted by the scientific community that at least two α -adrenergic receptors-- α_1 and α_2 --existed in the central and peripheral nervous systems. Since 1988, new techniques in molecular biology have led to the identification of at least six α -adrenergic receptors which exist throughout the central and peripheral nervous systems: α_{1A} (new nomenclature), α_{1B} , α_{1D} (new nomenclature), α_{2A} , α_{2B} and α_{2C} (Bylund, D.B., FASEB J., 6, 832 (1992)). In many cases,

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it is not known precisely which physiological responses in the body are controlled by each of these receptors. In addition, current α -adrenergic drugs are not selective for any particular α -adrenergic receptor.

5 Many of these drugs produce untoward side effects which may be attributed to their poor α -adrenergic receptor selectivity.

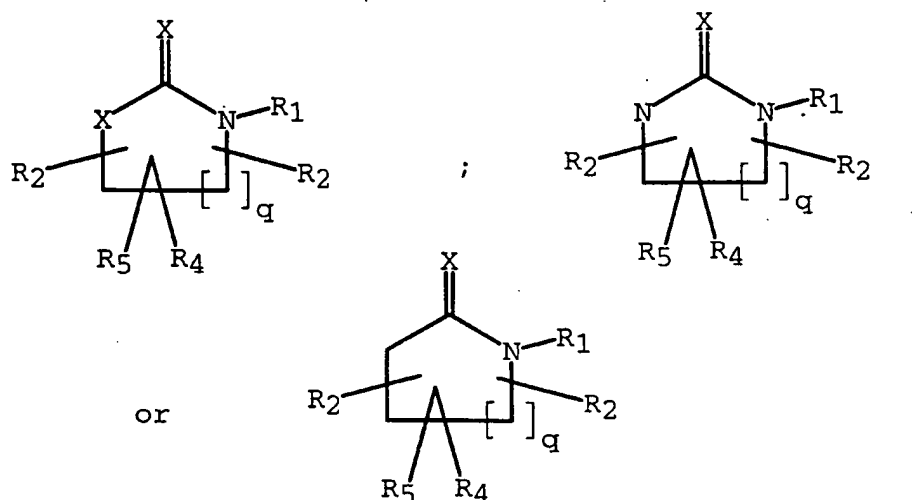
10 Since the mid 1970's, nonselective α -antagonists have been prescribed to treat BPH. In 1976, M. Caine, et al. (Brit. J. Urol., 48, 255 (1976)), reported that the nonselective α -antagonist phenoxybenzamine was useful in relieving the symptoms of BPH. This drug may produce its effects by interacting with α -receptors located on
15 the prostate. However, this drug also produces significant side effects such as dizziness and asthenia which severely limit its use in treating patients on a chronic basis. More recently, the α -adrenergic antagonists prazosin and terazosin have also been found
20 to be useful for treating BPH. However, these drugs also produce untoward side effects. It has recently been discovered that the α_{1A} receptor is responsible for mediating the contraction of human prostate smooth muscle (Gluchowski, C. et. al., WO 94/10989, 1994;
25 Forray, C. et. al., Mol. Pharmacol. 45, 703, 1994). This discovery indicates that the α_{1A} antagonists may be effective agents for the treatment of BPH with decreased side effects. Further studies have indicated that the α_{1A} receptor may also be present in other lower urinary
30 tract tissues, such as urethral smooth muscle (Ford et al. Br. J. Pharmacol., 114, 24P, (1995)).

This invention is directed to oxazolidinone compounds which are selective antagonists for cloned human α_{1A}
35 receptors. This invention is also related to uses of

these compounds for lowering intraocular pressure (Zhan, et. al. Ophthalmol. Vis. Sci., 34 Abst. #1133, 928, 1993), inhibiting cholesterol synthesis (D'Eletto and Javitt, J. Cardiovascular Pharmacol., 13 (Suppl. 2) S1-S4, 1989), benign prostatic hyperplasia, impotency (Milne and Wyllie, EP 0 459 666 A2, 1991), sympathetically mediated pain (Campbell, WO 92/14453, 1992), cardiac arrhythmia (Spiers, et. al., J. Cardiovascular Pharmacol., 16, 824-830, 1990) and for the treatment of any disease where antagonism of the α_{1A} receptor may be useful.

Summary of the Invention

This invention is directed to a compound having the structure:



5

wherein each X is independently O or S;

wherein q is 1 or 2;

10

wherein each R₂ is independently H; -(CH₂)_tXR₃; -(CH₂)_tC(X)NR₃; -(CH₂)_tCO₂R₃; -CO₂R₃; straight chained or branched C₁-C₇ alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

15

wherein each t is an integer from 1 to 4 inclusive;

20

wherein each R₃ is independently H; straight chained or branched C₁-C₇ alkyl, straight chained or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇

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cycloalkenyl;

wherein R_4 is aryl, heteroaryl, C_1 - C_7 alkyl substituted with one or two aryl, or C_1 - C_7 alkyl substituted with
5 one or two heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, $-\text{NO}_2$, $-\text{N}(\text{R}_3)_2$, $-\text{COR}_3$, $-(\text{CH}_2)_t\text{XR}_3$, $-(\text{CH}_2)_n\text{C}(\text{X})\text{NR}_3$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or
10 straight chained or branched C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

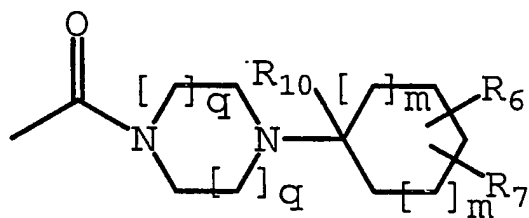
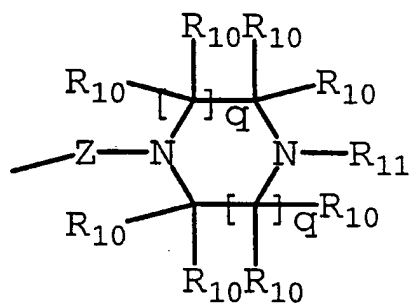
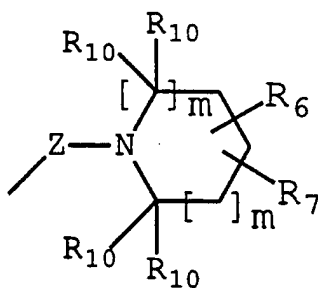
wherein each n independently is an integer from 0 to 7 inclusive;

15 wherein R_5 is H; aryl, C_1 - C_7 alkyl substituted with aryl, heteroaryl, or C_1 - C_7 alkyl substituted with heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, $-\text{NO}_2$, $-\text{N}(\text{R}_3)_2$, $-\text{COR}_3$, $-(\text{CH}_2)_t\text{XR}_3$, $-(\text{CH}_2)_n\text{C}(\text{X})\text{NR}_3$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_3$, straight chained or
20 branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or straight chained or branched C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

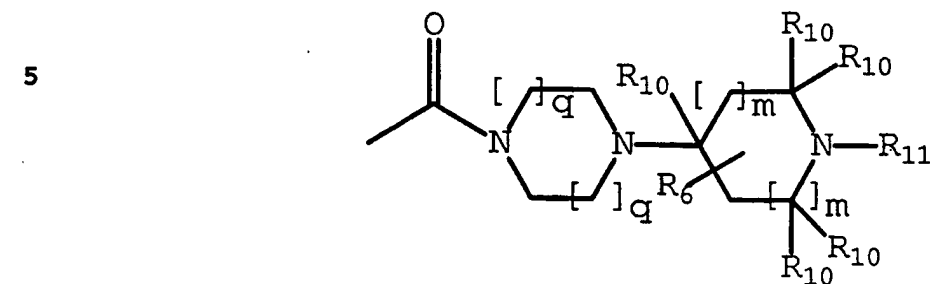
25 where R_5 and one R_2 on adjacent carbon atoms together may form aryl, heteroaryl, indane or tetrahydronaphthyl, C_3 - C_7 cycloalkyl, or heterocycloalkyl wherein one or two heteroatoms may be O, N or S;

30

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wherein R_1 is

or



where each R_6 is independently H; straight chained or
 15 branched C_1 - C_7 , alkyl, hydroxyalkyl, aminoalkyl,
 alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl;
 straight chained or branched C_2 - C_7 , alkenyl or alkynyl;
 C_3 - C_7 , cycloalkyl, monofluorocycloalkyl,
 polyfluorocycloalkyl or cycloalkenyl; aryl or
 20 heteroaryl, wherein the aryl or heteroaryl may be
 substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$,
 $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-$
 SO_2R_3 , straight chained or branched C_1 - C_7 , alkyl,
 monofluoroalkyl or polyfluoroalkyl, straight chained or
 25 branched C_2 - C_7 , alkenyl or alkynyl, or C_3 - C_7 , cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or C_5 - C_7 ,
 cycloalkenyl;

where each R_7 is independently H; F; Cl; Br; I; $-COR_3$; $-$
 30 CO_2R_3 ; $-(CH_2)_nXR_3$; $-COR_3$; $-(CH_2)_nC(X)N(R_3)_2$; $-(CH_2)_nCO_2R_3$; $-$
 CN ; $-NO_2$; $-N(R_3)_2$; straight chained or branched C_1 - C_7 ,
 alkyl, hydroxyalkyl, aminoalkyl, carboxamidoalkyl,
 alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl;
 straight chained or branched C_2 - C_7 , alkenyl or alkynyl;
 35 C_3 - C_7 , cycloalkyl, monofluorocycloalkyl,

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polyfluorocycloalkyl or C₅-C₇ cycloalkenyl, wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -(CH₂)_nXR₃, -COR₃, -(CH₂)_nC(X)N(R₃)₂, -(CH₂)_nCO₂R₃, -CN, -NO₂, -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -(CH₂)_nXR₃, -COR₃, -(CH₂)_nC(X)N(R₃)₂, -(CH₂)_nCO₂R₃, -CN, -NO₂, -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl;

wherein each R₁₀ is independently H; (CH₂)_tXR₃; (CH₂)_tC(X)NR₃; (CH₂)_tCO₂R₃; straight chained or branched C₁-C₇ alkyl or carboxamidoalkyl; straight chained or branched C₂-C₇ aminoalkyl, alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

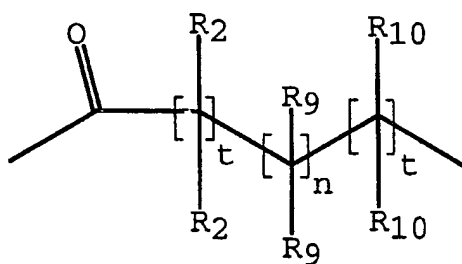
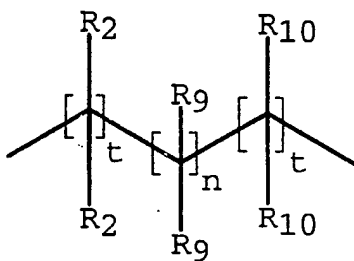
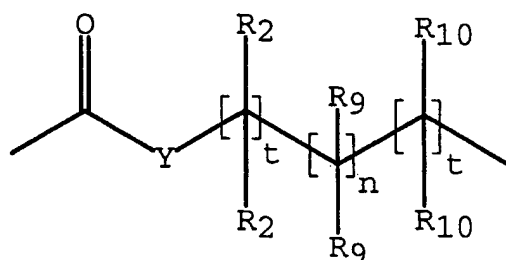
wherein R₁₁ is aryl, heteroaryl, C₁-C₇ alkyl substituted with one or two aryl, or C₁-C₇ alkyl substituted with one or two heteroaryl; wherein any aryl or heteroaryl independently may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -N(R₃)₂, -COR₃, -(CH₂)_nXR₃, -(CH₂)_nC(X)NR₃, -(CH₂)_nCO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, or carboxamidoalkyl, straight chained or branched C₂-C₇

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aminoalkyl, alkenyl, or alkynyl, or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

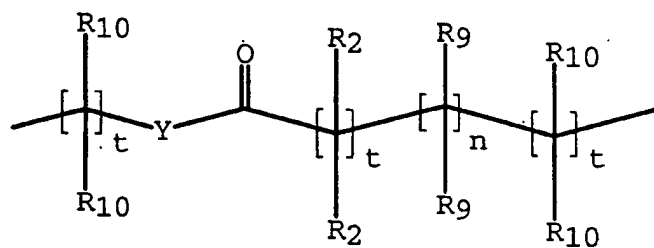
wherein each m independently is an integer from 0 to 3 inclusive;

wherein Z is



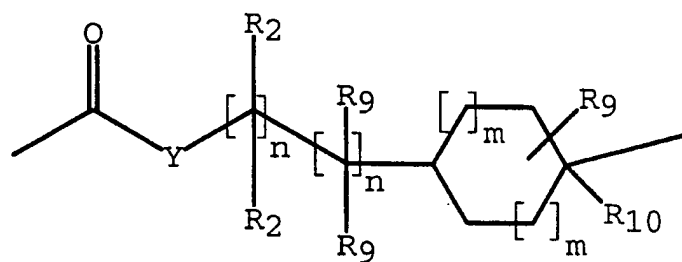
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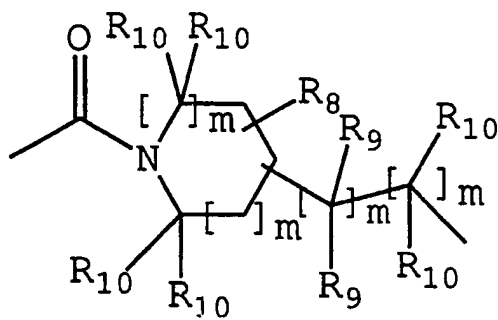
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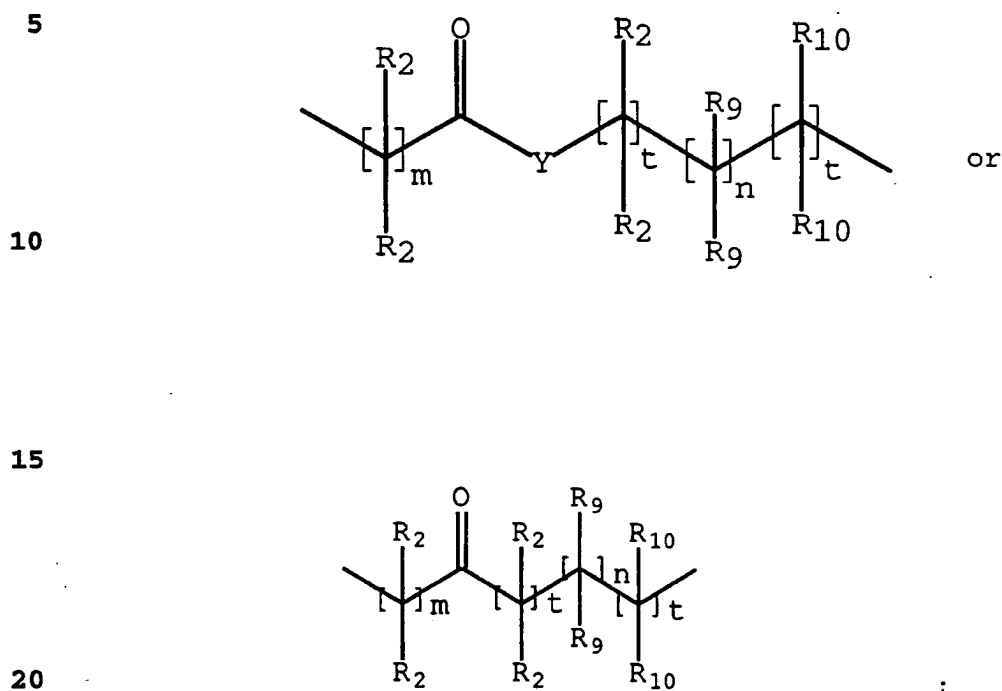


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25 or C₂-C₇ alkenyl, wherein the C₂-C₇ alkenyl may be unsubstituted or substituted with one or more R₉ groups;

30 where R₈ is H; (CH₂)_tXR₃; (CH₂)_tC(X)NR₃; (CH₂)_tCO₂R₃; straight chained or branched C₁-C₇ alkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ aminoalkyl, alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

35 where each R₉ is independently H; F; Cl; Br; I; (CH₂)_mXR₃; (CH₂)_mC(X)NR₃; (CH₂)_mCO₂R₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl,

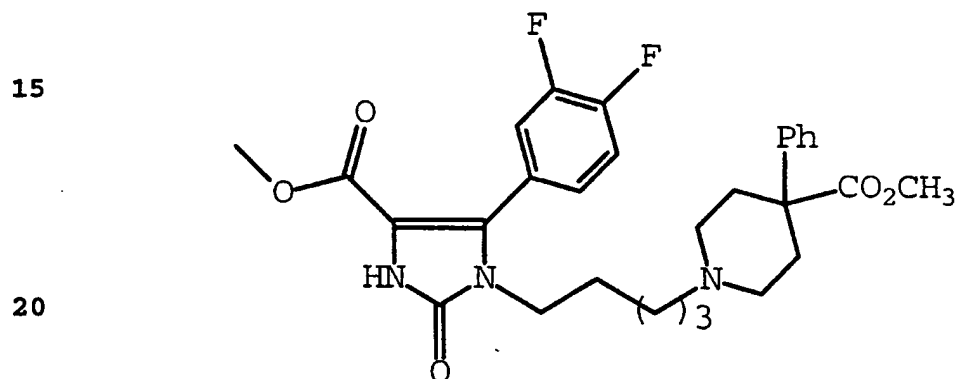
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aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C, alkenyl, or alkynyl; or C₃-C, cycloalkyl or C₅-C, cycloalkenyl;

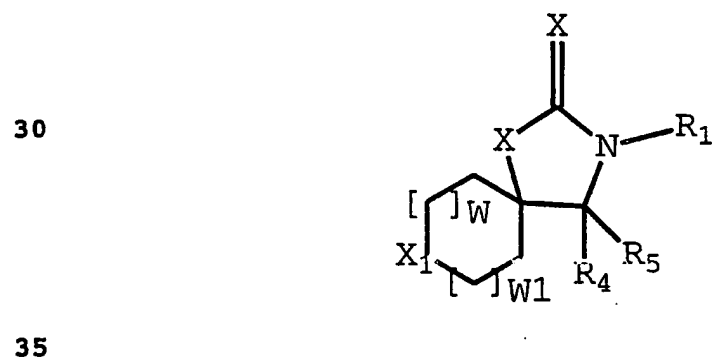
5 wherein Y is S, O, or NR₈;

or a pharmaceutically acceptable salt thereof.

10 The present invention is additionally directed to a compound having the structure:



25 This invention is additionally directed to a compound having the structure:



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wherein each W is an integer from 0 to 3 inclusive;

wherein each W1 is an integer from 0 to 3 inclusive;

5 wherein each X is independently O or S;

wherein X1 is O, S, NR₃;

10 wherein each R₂ is independently H; -(CH₂)_tXR₃; -
(CH₂)_tC(X)NR₃; -(CH₂)_tCO₂R₃; -CO₂R₃; straight chained or
branched C₁-C₇ alkyl, aminoalkyl, carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, or
alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

15 wherein each t is an integer from 1 to 4 inclusive;

20 wherein each R₃ is independently H; straight chained
or branched C₁-C₇ alkyl, straight chained or branched
C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇
cycloalkenyl;

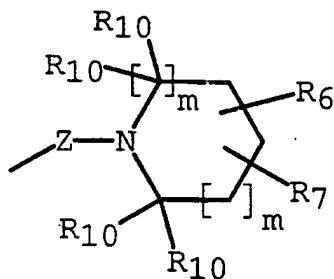
25 wherein R₄ is aryl, heteroaryl, C₁-C₇ alkyl substituted
with one or two aryl, or C₁-C₇ alkyl substituted with
one or two heteroaryl; wherein the aryl or heteroaryl
may be substituted with one or more of F, Cl, Br, I, -
CN, -NO₂, -N(R₃)₂, -COR₃, -(CH₂)_tXR₃, -(CH₂)_nC(X)NR₃, -
(CH₂)_nCO₂R₃, straight chained or branched C₁-C₇ alkyl,
monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl,
or straight chained or branched C₂-C₇ aminoalkyl,
30 alkenyl or alkynyl, or C₃-C₇ cycloalkyl or C₅-C₇
cycloalkenyl;

35 wherein each n independently is an integer from 0 to 7
inclusive;

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wherein R_5 is H; aryl, C_1 - C_7 alkyl substituted with aryl, heteroaryl, or C_1 - C_7 alkyl substituted with heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -
 5 NO_2 , $-N(R_3)_2$, $-COR_3$, $-(CH_2)_tXR_3$, $-(CH_2)_nC(X)NR_3$, $-(CH_2)_nCO_2R_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or straight chained or branched C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7
 10 cycloalkenyl;

wherein R_1 is



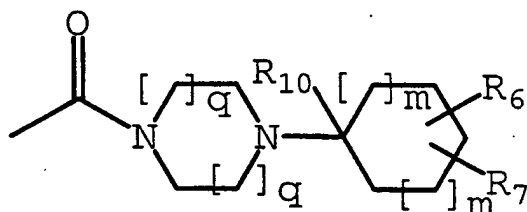
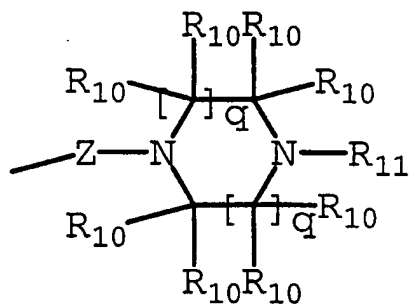
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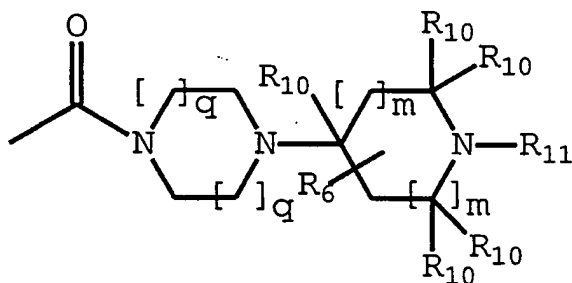
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or



where each R_6 is independently H; straight chained or branched C_1 -C, alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 -C, alkenyl or alkynyl; C_3 -C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 -C, cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$,

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5 -COR₃, -(CH₂)_nC(X)N(R₃)₂, -(CH₂)_nCO₂R₃, -CN, -NO₂, -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl;

10 where each R₇ is independently H; F; Cl; Br; I; -COR₃; -CO₂R₃; -(CH₂)_nXR₃; (CH₂)_nC(X)N(R₃)₂; -(CH₂)_nCO₂R₃; -CN; -NO₂; -N(R₃)₂; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl, carboxamidoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl, wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -(CH₂)_nXR₃,
 20 -COR₃, -(CH₂)_nC(X)N(R₃)₂, -(CH₂)_nCO₂R₃, -CN, -NO₂, -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl;
 25 aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -(CH₂)_nXR₃, -COR₃, -(CH₂)_nC(X)N(R₃)₂, -(CH₂)_nCO₂R₃, -CN, -NO₂, -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl;

35 wherein each R₁₀ is independently H; (CH₂)_tXR₃;

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$(\text{CH}_2)_t\text{C}(\text{X})\text{NR}_3$; $(\text{CH}_2)_t\text{CO}_2\text{R}_3$; straight chained or branched C_1 - C_7 alkyl or carboxamidoalkyl; straight chained or branched C_2 - C_7 aminoalkyl, alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

5

wherein R_{11} is aryl, heteroaryl, C_1 - C_7 alkyl substituted with one or two aryl, or C_1 - C_7 alkyl substituted with one or two heteroaryl; wherein any aryl or heteroaryl independently may be substituted with one or more of F, Cl, Br, I, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}(\text{R}_3)_2$, $-\text{COR}_3$, $-(\text{CH}_2)_n\text{XR}_3$, $-(\text{CH}_2)_n\text{C}(\text{X})\text{NR}_3$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, or carboxamidoalkyl, straight chained or branched C_2 - C_7 aminoalkyl, alkenyl, or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

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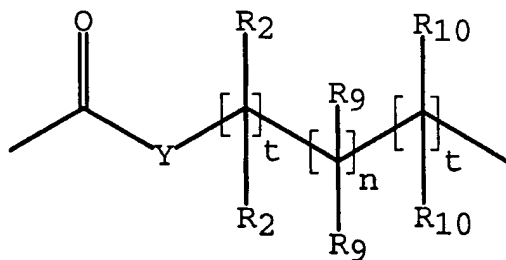
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wherein each m independently is an integer from 0 to 3 inclusive;

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wherein Z is

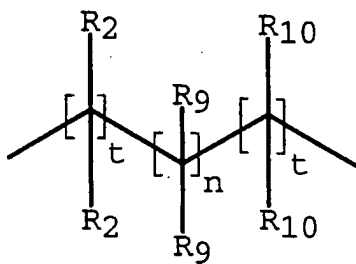
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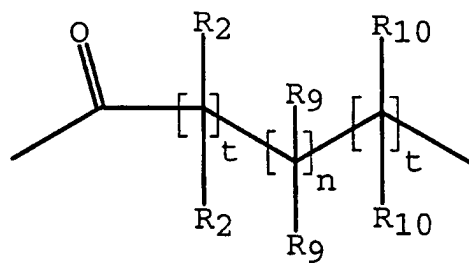
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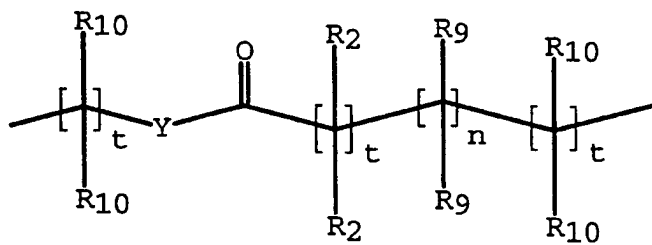
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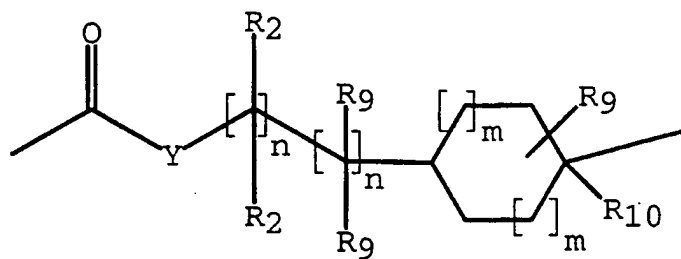
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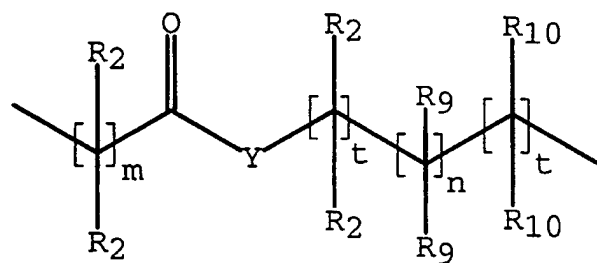
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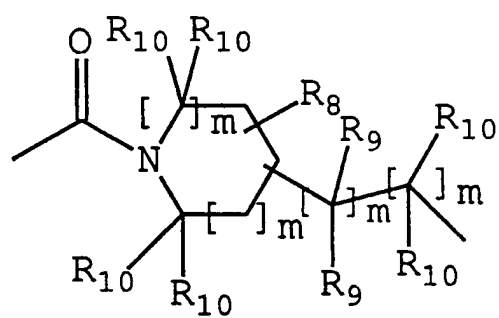
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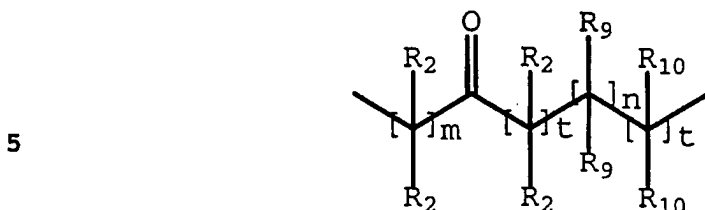


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or

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-22-



or C₂-C₇ alkenyl, wherein the C₂-C₇ alkenyl may be
 10 unsubstituted or substituted with one or more R₉ groups;

where R₈ is H; (CH₂)_tXR₃; (CH₂)_tC(X)NR₃; (CH₂)_tCO₂R₃;
 straight chained or branched C₁-C₇ alkyl,
 carboxamidoalkyl; straight chained or branched C₂-C₇
 15 aminoalkyl, alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or
 C₅-C₇ cycloalkenyl;

where each R₉ is independently H; F; Cl; Br; I;
 (CH₂)_mXR₃; (CH₂)_mC(X)NR₃; (CH₂)_mCO₂R₃; straight chained or
 20 branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl,
 aminoalkyl, or carboxamidoalkyl; straight chained or
 branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl
 or C₅-C₇ cycloalkenyl;

25 wherein Y is S, O, or NR₈;

or a pharmaceutically acceptable salt thereof.

This invention is also related to uses of these
 30 compounds for lowering intraocular pressure, inhibiting
 cholesterol synthesis, relaxing lower urinary tract
 tissue, the treatment of benign prostatic hyperplasia,
 impotency, cardiac arrhythmia and for the treatment of
 any disease where antagonism of the α_{1A} receptor may be
 35 useful. The invention further provides pharmaceutical

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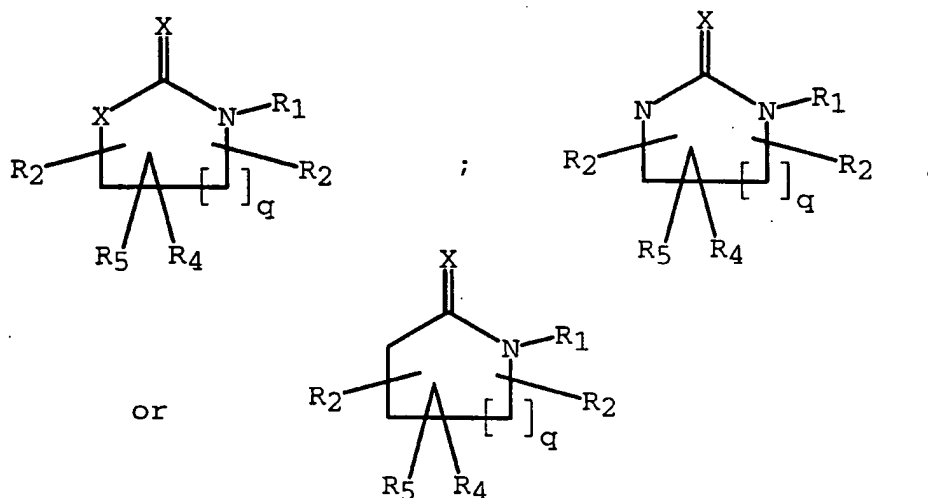
compositions comprising a therapeutically effective amount of the above-defined compounds and a pharmaceutically acceptable carrier.

Brief Description of the Figures

Figure 1 Figures 1A-1M show the structures of the
compounds described hereinbelow in the
Examples.

Detailed Description of the Invention

The present invention is directed to compounds having the structure:



5

wherein each X is independently O or S;

wherein q is 1 or 2;

10

wherein each R_2 is independently H ; $-(CH_2)_tXR_3$; $-(CH_2)_tC(X)NR_3$; $-(CH_2)_tCO_2R_3$; $-CO_2R_3$; straight chained or branched C_1 - C_7 alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C_2 - C_7 alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

15

wherein each t is an integer from 1 to 4 inclusive;

20

wherein each R₃ is independently H; straight chained or branched C₁-C₇ alkyl, straight chained or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇

cycloalkenyl;

5 wherein R_4 is aryl, heteroaryl, C_1 - C_7 alkyl substituted with one or two aryl, or C_1 - C_7 alkyl substituted with one or two heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -N(R₃)₂, -COR₃, -(CH₂)_tXR₃, -(CH₂)_nC(X)NR₃, -(CH₂)_nCO₂R₃, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or
10 straight chained or branched C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

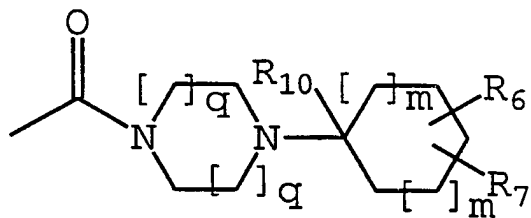
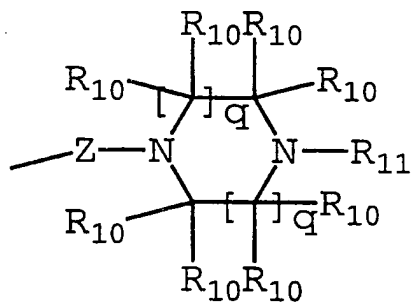
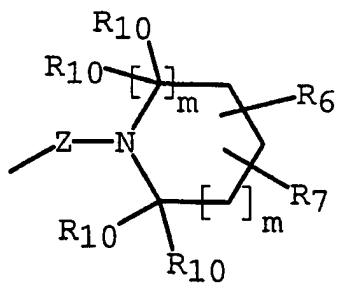
wherein each n independently is an integer from 0 to 7 inclusive;

15 wherein R_5 is H; aryl, C_1 - C_7 alkyl substituted with aryl, heteroaryl, or C_1 - C_7 alkyl substituted with heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -N(R₃)₂, -COR₃, -(CH₂)_tXR₃, -(CH₂)_nC(X)NR₃, -(CH₂)_nCO₂R₃, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or straight chained or branched C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

25 where R_5 and one R_2 on adjacent carbon atoms together may form aryl, heteroaryl, indane or tetrahydronaphthyl, C_3 - C_7 cycloalkyl, or heterocycloalkyl wherein one or two heteroatoms may be O, N or S;

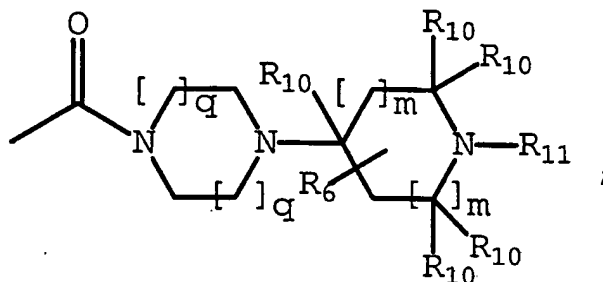
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-27-

wherein R_1 is

or

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where each R₆ is independently H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl;
 15 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -(CH₂)_nXR₃, -COR₃, -(CH₂)_nC(X)N(R₃)₂, -(CH₂)_nCO₂R₃, -CN, -NO₂, -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl;
 25

where each R₇ is independently H; F; Cl; Br; I; -COR₃; -CO₂R₃; -(CH₂)_nXR₃; -COR₃; -(CH₂)_nC(X)N(R₃)₂; -(CH₂)_nCO₂R₃; -CN; -NO₂; -N(R₃)₂; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl, carboxamidoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl;
 30 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl, wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl,
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- cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, -
- 5 CN, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5-C_7 cycloalkenyl; aryl or
- 10 heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, -CN, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl or
- 15 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5-C_7 cycloalkenyl;
- 20 wherein each R_{10} is independently H; $(CH_2)_tXR_3$; $(CH_2)_tC(X)NR_3$; $(CH_2)_tCO_2R_3$; straight chained or branched C_1-C_7 alkyl or carboxamidoalkyl; straight chained or branched C_2-C_7 aminoalkyl, alkenyl, or alkynyl; or C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl;
- 25 wherein R_{11} is aryl, heteroaryl, C_1-C_7 alkyl substituted with one or two aryl, or C_1-C_7 alkyl substituted with one or two heteroaryl; wherein any aryl or heteroaryl independently may be substituted with one or more of F,
- 30 Cl, Br, I, -CN, $-NO_2$, $-N(R_3)_2$, $-COR_3$, $-(CH_2)_nXR_3$, $-(CH_2)_nC(X)NR_3$, $-(CH_2)_nCO_2R_3$, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, or carboxamidoalkyl, straight chained or branched C_2-C_7 aminoalkyl, alkenyl, or alkynyl, or C_3-C_7 cycloalkyl or
- 35 C_5-C_7 cycloalkenyl;

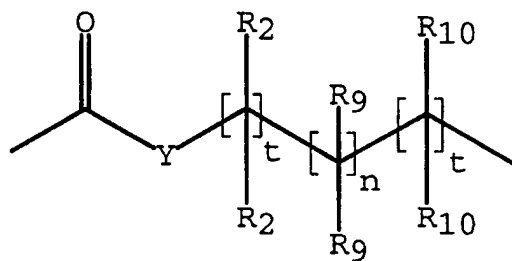
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wherein each m independently is an integer from 0 to 3 inclusive;

wherein Z is

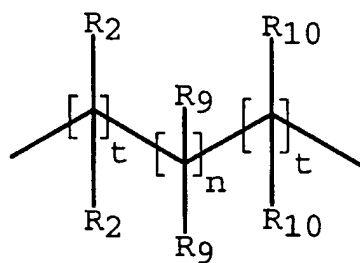
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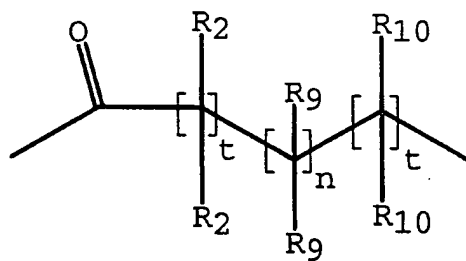
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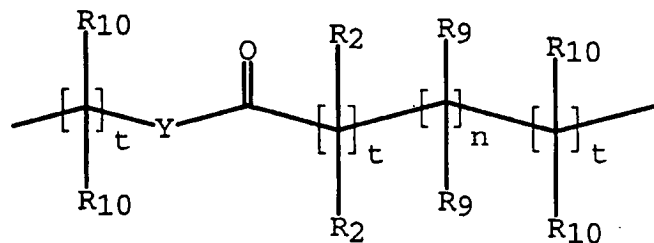
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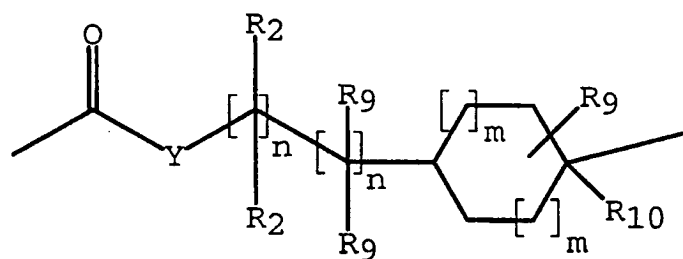
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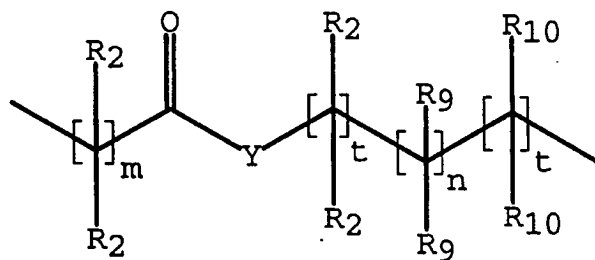
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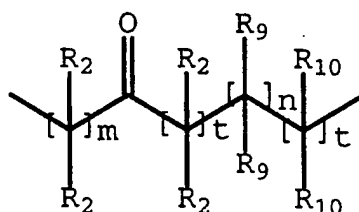
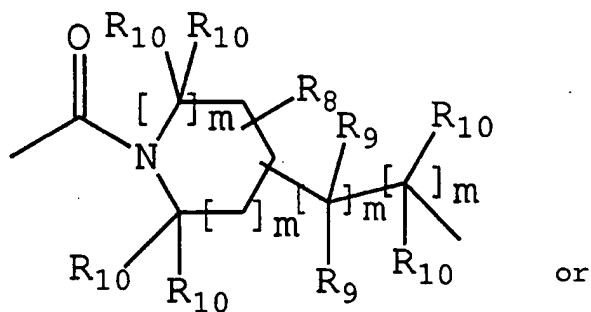
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or C₂-C₇ alkenyl, wherein the C₂-C₇ alkenyl may be
 20 unsubstituted or substituted with one or more R₉ groups;

where R₈ is H; (CH₂)_tXR₃; (CH₂)_tC(X)NR₃; (CH₂)_tCO₂R₃;
 straight chained or branched C₁-C₇ alkyl,
 carboxamidoalkyl; straight chained or branched C₂-C₇
 25 aminoalkyl, alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or
 C₅-C₇ cycloalkenyl;

where each R₉ is independently H; F; Cl; Br; I;
 (CH₂)_mXR₃; (CH₂)_mC(X)NR₃; (CH₂)_mCO₂R₃; straight chained or
 30 branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl,
 aminoalkyl, or carboxamidoalkyl; straight chained or
 branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl
 or C₅-C₇ cycloalkenyl;

35 wherein Y is S, O, or NR₈;

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or a pharmaceutically acceptable salt thereof.

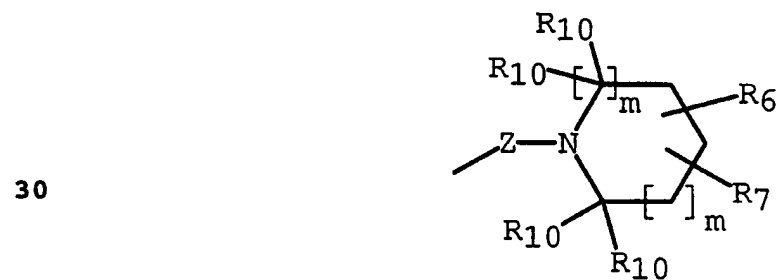
The invention further provides for the (+) enantiomer of any of the compounds described herein which may be a *cis* isomer or a *trans* isomer. The invention also provides
 5 for the (-) enantiomer of any of the compounds described herein which may be a *cis* or a *trans* isomer.

The compounds of the present invention are preferably at
 10 least 80% pure, more preferably at least 90% pure, and most preferably at least 95% pure.

In the present invention the term "aryl" is used to include phenyl, benzyl, benzoyl or naphthyl and the term
 15 "heteroaryl" is used to include pyrazinyl, pyrrolyl, furanyl, thiophenyl, pyridyl, imidazolyl, indolyl, aminophenyl, benzamidyl, benzimidazolyl, benzfurazanyl, benzfuranyl, 2-keto-1-benzimidazolyl or quinolyl.

The compounds of this invention exhibit at least ten-fold greater affinity for the human α_{1A} receptor than for the human α_{1B} or human α_{1D} receptor.

In one embodiment of the present invention R_1 is
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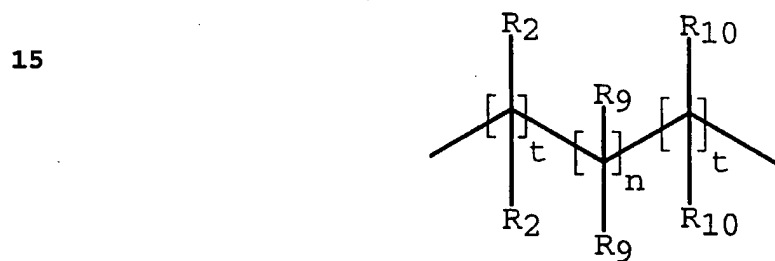
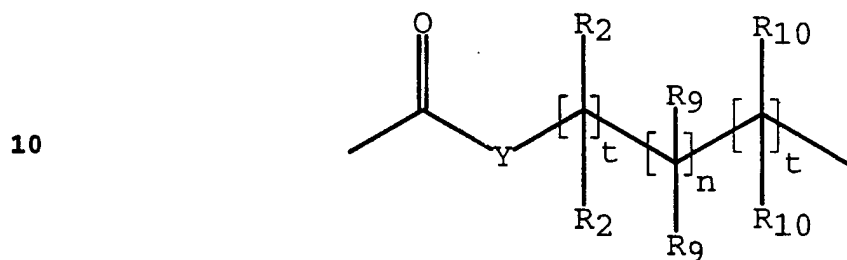


35 R_4 is aryl or heteroaryl, where the aryl may be

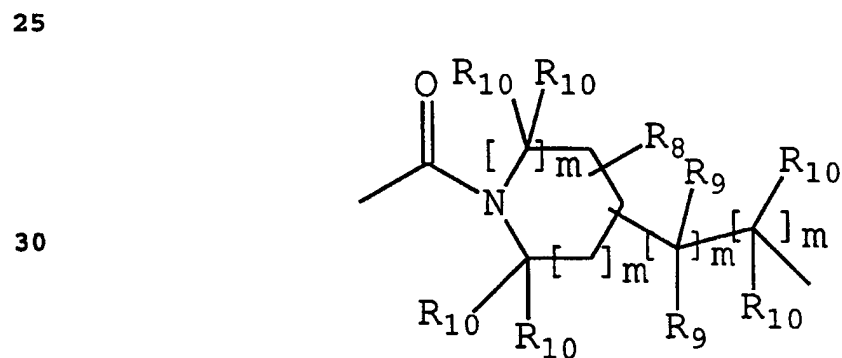
-34-

substituted with one or more of F, Cl, $-(CH_2)_tOR_3$, $-(CH_2)_nCONR_3$, $-(CH_2)_nCO_2R_3$, straight chained or branched C_1 - C_7 alkyl or monofluoroalkyl; and

5 Z is



or



In another embodiment of the present invention R_4 is
 35 pyridyl or phenyl, where the phenyl may be substituted

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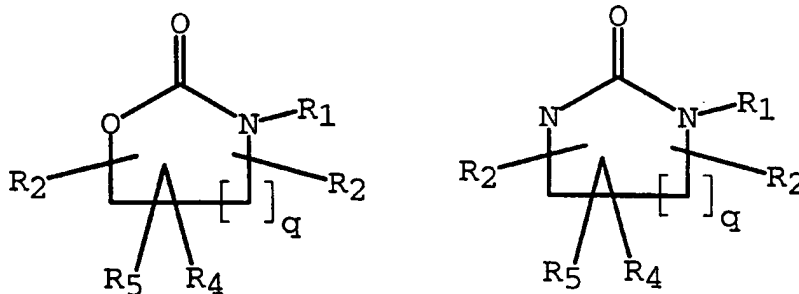
with one or more of F, Cl, $-(CH_2)_tOR_3$, $-(CH_2)_nC(O)NR_3$, $-(CH_2)_nCO_2R_3$, straight chained or branched C_1 - C_7 alkyl or monofluoroalkyl.

- 5 In yet another embodiment of the present invention each R_6 is independently aryl or heteroaryl, where the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained
 10 or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl.

- In a further embodiment of the present invention R_7 is
 15 H; $-CN$; $-CO_2R_3$; $-C(O)NR_3$; $-(CH_2)_mXR_3$; unsubstituted or substituted aryl; C_1 - C_3 alkyl; or $-OCOR_3$.

- In another embodiment of the present invention R_4 is
 20 phenyl which may be substituted with at least one of F or Cl.

In yet another embodiment of the present invention the compound has the structure:

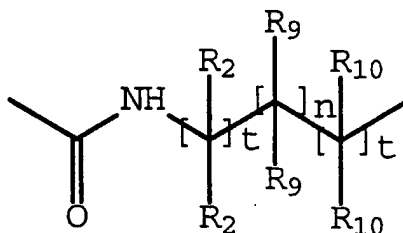


or

In another embodiment of the present invention Z is:

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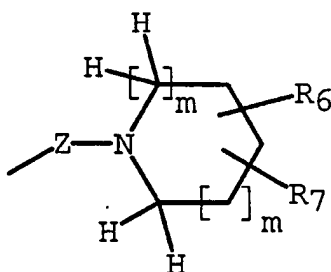


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In a further embodiment of the present invention q is 1 and R_1 is

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In a further embodiment of the present invention at least one R_2 is C_1 - C_3 alkyl.

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In another embodiment of the present invention R_4 is phenyl substituted with at least one of F or Cl.

5 In a further embodiment of the present invention R_4 is phenyl substituted with at least two F.

In an embodiment of the present invention R_4 is 3,4-difluorophenyl.

10 In an additional embodiment of the present invention R_6 is pyridyl, phenyl, or phenyl substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1-C_7 alkyl,
15 monofluoroalkyl or polyfluoroalkyl.

In a further embodiment of the present invention R_7 is H; $-CN$; or $-CO_2R_3$.

20 In another embodiment of the present invention R_9 is F; $-OH$; C_1-C_3 alkyl; or $-(CH_2)_mXR_3$.

In an embodiment, when R_9 is $-OH$ or F, the other R_9 on the same carbon atom is not $-OH$. In yet another
25 embodiment, when R_9 is F, the other R_9 on the same carbon atom is C_1-C_3 alkyl, F, Cl, Br, or I.

In yet another embodiment of the present invention R_6 is 4-fluorophenyl.

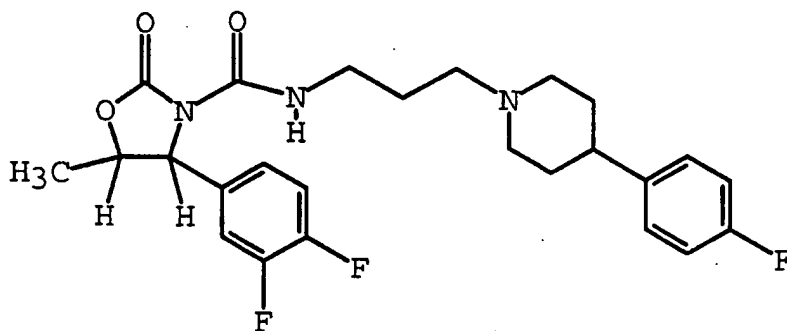
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In one embodiment of the invention,
the compound is a *trans* (+) isomer having the structure:

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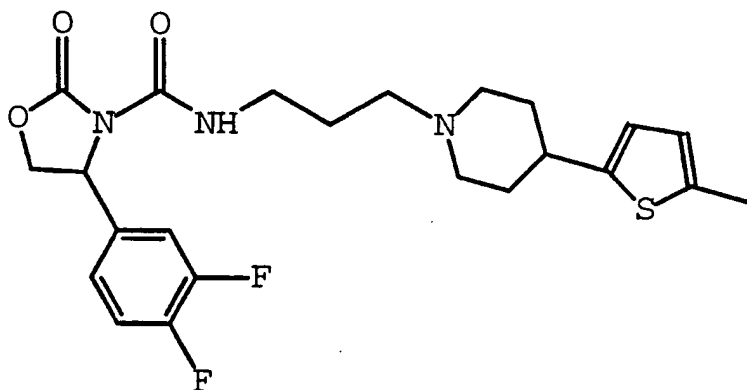


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This invention is additionally directed to a compound having the structure:

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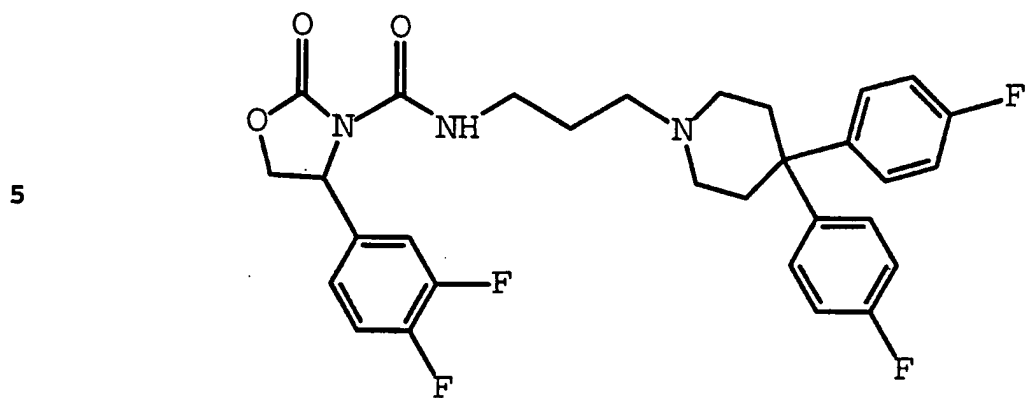


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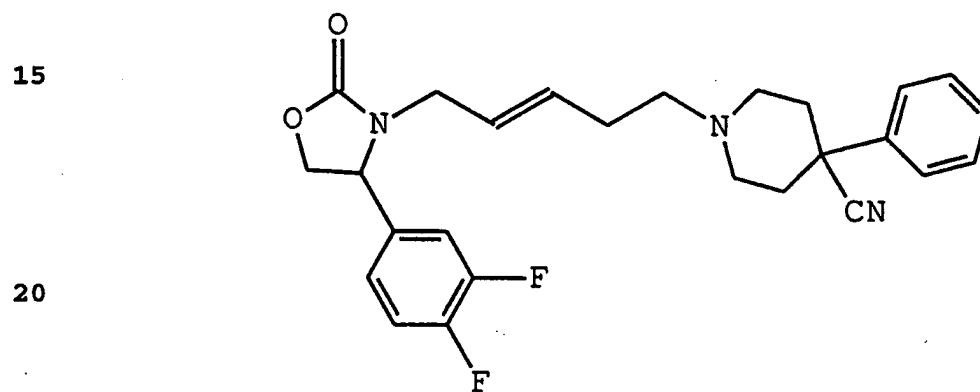
This invention is additionally directed to a compound having the structure:

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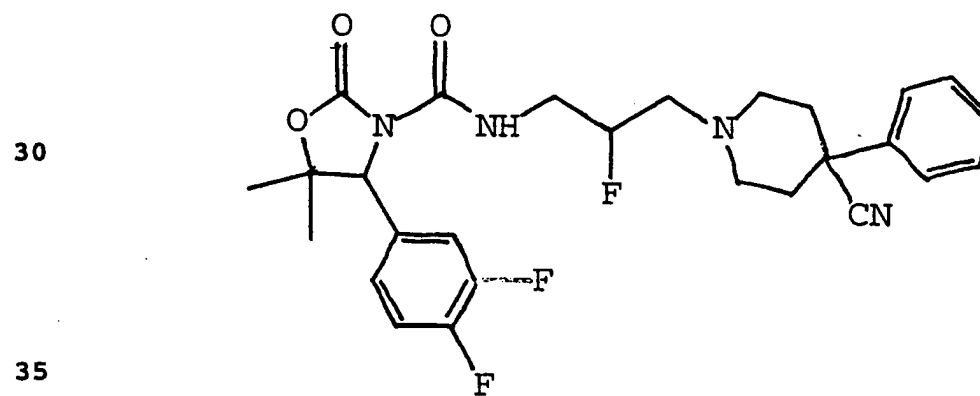
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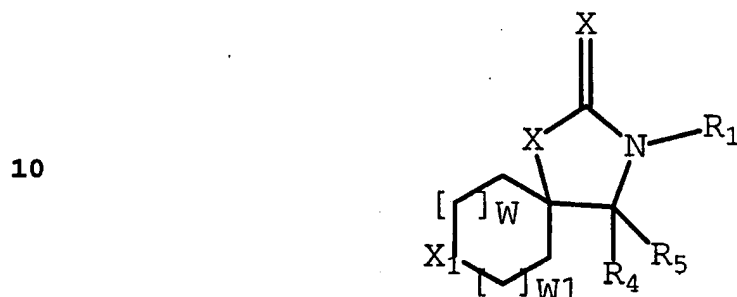
This invention is additionally directed to a compound having the structure:



This invention is additionally directed to a compound having the structure:



5 This invention includes a compound having the structure:



15 wherein each W is an integer from 0 to 3 inclusive;

wherein each W1 is an integer from 0 to 3 inclusive;

wherein each X is independently O or S;

20

wherein each X1 is O, S, NR₃;

wherein each R₂ is independently H; -(CH₂)_tXR₃; -

25

(CH₂)_tC(X)NR₃; -(CH₂)_tCO₂R₃; -CO₂R₃; straight chained or branched C₁-C₇ alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

wherein each t is an integer from 1 to 4 inclusive;

30

wherein each R₃ is independently H; straight chained or branched C₁-C₇ alkyl, straight chained or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

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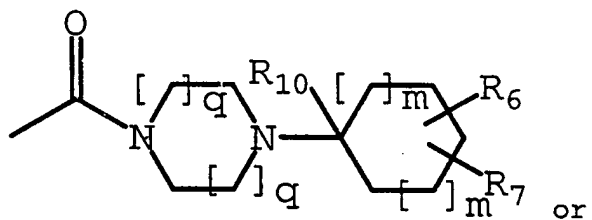
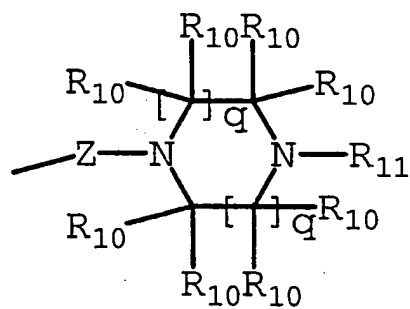
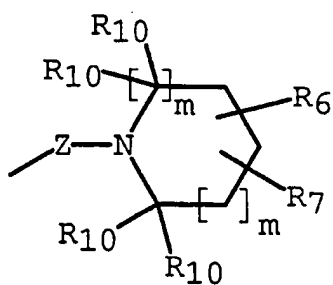
-41-

wherein R_4 is aryl, heteroaryl, C_1 - C_7 alkyl substituted with one or two aryl, or C_1 - C_7 alkyl substituted with one or two heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, - NO_2 , - $N(R_3)_2$, - COR_3 , - $(CH_2)_tXR_3$, - $(CH_2)_nC(X)NR_3$, - $(CH_2)_nCO_2R_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or straight chained or branched C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

wherein each n independently is an integer from 0 to 7 inclusive;

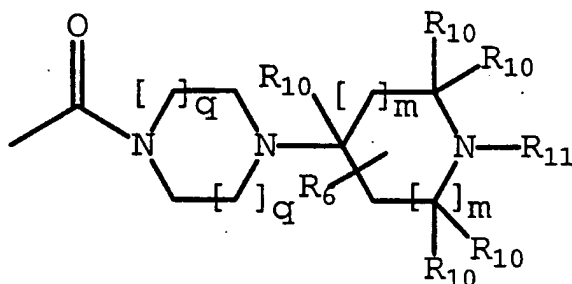
wherein R_5 is H; aryl, C_1 - C_7 alkyl substituted with aryl, heteroaryl, or C_1 - C_7 alkyl substituted with heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, - NO_2 , - $N(R_3)_2$, - COR_3 , - $(CH_2)_tXR_3$, - $(CH_2)_nC(X)NR_3$, - $(CH_2)_nCO_2R_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or straight chained or branched C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

wherein R_1 is



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wherein each R_6 is independently H; straight chained or branched C_1 -C, alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 -C, alkenyl or alkynyl; C_3 -C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 -C, cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -
 (CH₂)_nXR₃, -COR₃, -(CH₂)_nC(X)N(R₃)₂, -(CH₂)_nCO₂R₃, -CN, -NO₂, -N(R₃)₂, -SO₂R₃; straight chained or branched C_1 -C, alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2 -C, alkenyl or alkynyl, or C_3 -C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 -C, cycloalkenyl;

wherein each R_7 is independently H; F; Cl; Br; I; -COR₃; -CO₂R₃; -(CH₂)_nXR₃; (CH₂)_nC(X)N(R₃)₂; -(CH₂)_nCO₂R₃; -CN; -NO₂; -N(R₃)₂; straight chained or branched C_1 -C, alkyl, hydroxyalkyl, aminoalkyl, carboxamidoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 -C, alkenyl or alkynyl; C_3 -C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 -C, cycloalkenyl, wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl,

- alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5-C_7 cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5-C_7 cycloalkenyl;
- wherein each R_{10} is independently H; $(CH_2)_tXR_3$; $(CH_2)_tC(X)NR_3$; $(CH_2)_tCO_2R_3$; straight chained or branched C_1-C_7 alkyl or carboxamidoalkyl; straight chained or branched C_2-C_7 aminoalkyl, alkenyl, or alkynyl; or C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl;
- wherein R_{11} is aryl, heteroaryl, C_1-C_7 alkyl substituted with one or two aryl, or C_1-C_7 alkyl substituted with one or two heteroaryl; wherein any aryl or heteroaryl independently may be substituted with one or more of F, Cl, Br, I, $-CN$, $-NO_2$, $-N(R_3)_2$, $-COR_3$, $-(CH_2)_nXR_3$, $-(CH_2)_nC(X)NR_3$, $-(CH_2)_nCO_2R_3$, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, or carboxamidoalkyl, straight chained or branched C_2-C_7 aminoalkyl, alkenyl, or alkynyl, or C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl;

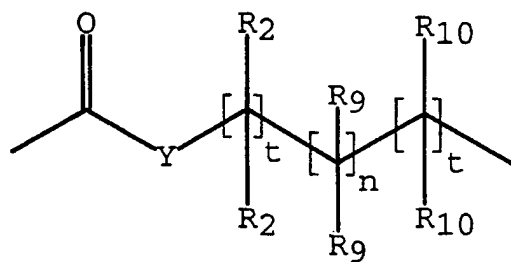
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wherein each m independently is an integer from 0 to 3 inclusive;

wherein Z is

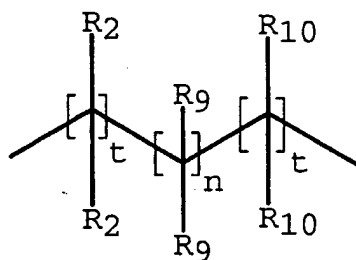
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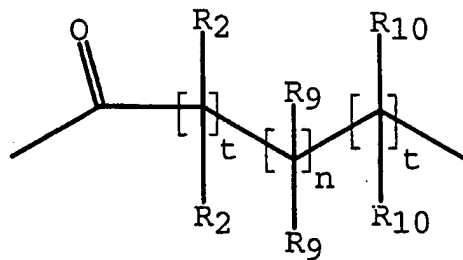
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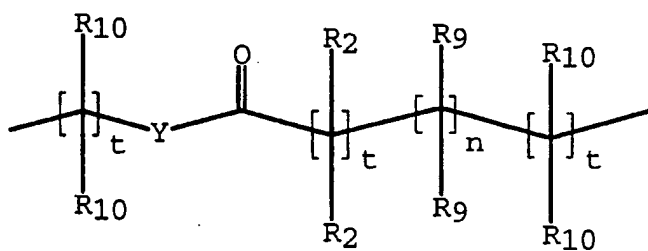
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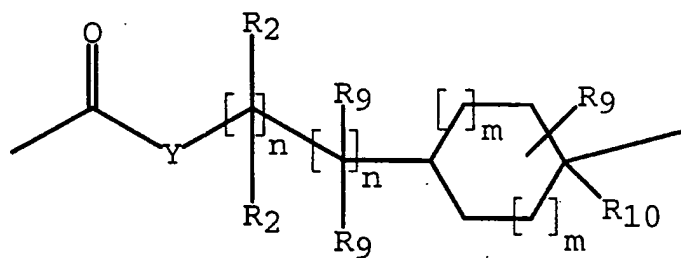
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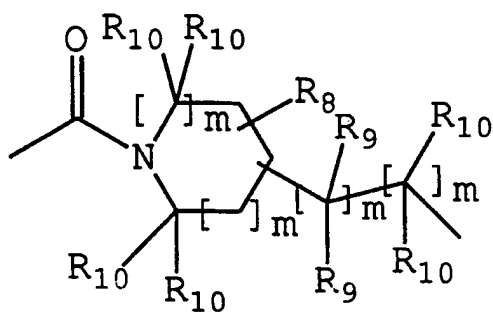
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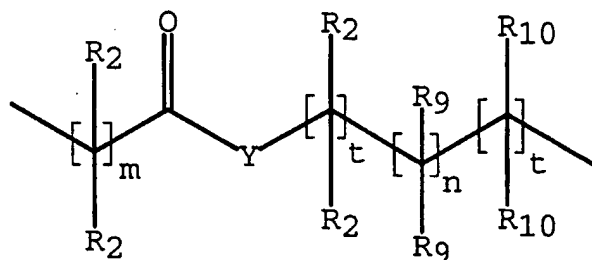
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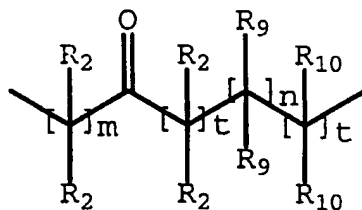
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or

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or C_2 - C_7 alkenyl, wherein the C_2 - C_7 alkenyl may be unsubstituted or substituted with one or more R_9 groups;

25

where R_8 is H; $(CH_2)_tXR_3$; $(CH_2)_tC(X)NR_3$; $(CH_2)_tCO_2R_3$; straight chained or branched C_1 - C_7 alkyl, carboxamidoalkyl; straight chained or branched C_2 - C_7 aminoalkyl, alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

30

where each R_9 is independently H; F; Cl; Br; I; $(CH_2)_mXR_3$; $(CH_2)_mC(X)NR_3$; $(CH_2)_mCO_2R_3$; straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C_2 - C_7 alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

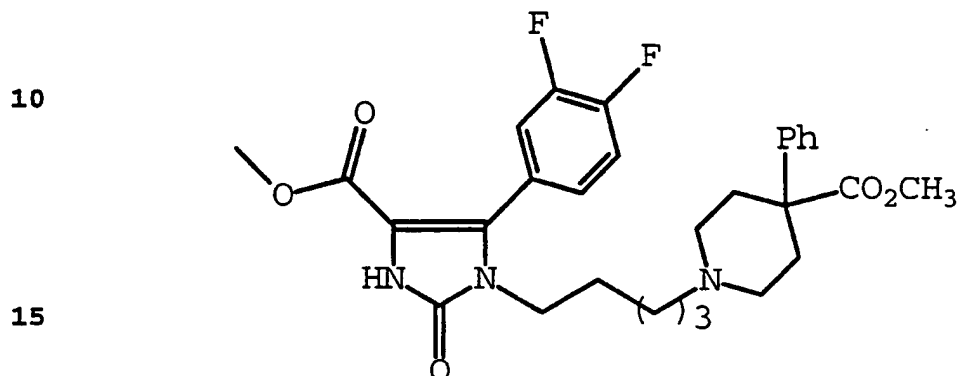
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-48-

wherein Y is S, O, or NR₈;

or a pharmaceutically acceptable salt thereof.

- 5 The present invention is additionally directed to a compound having the structure:



- 20 The invention also encompasses the (-) and (+) enantiomers of all compounds described herein. The invention further includes *cis* and *trans* isomers of all of the compounds described herein, the terms "*cis*" and "*trans*" corresponding to relative stereochemistry, as determined, for example, by NOE (Nuclear Overhauser Effect) experiments. In one embodiment, *cis* and *trans* designate the relative positions of aryl and alkyl on adjacent carbons in the oxazolidinone ring (see Examples 18 and 19).

- 30 Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The salts include but are not limited to the following acids and bases: inorganic acids such as hydrochloric acid, hydrofluoric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid;
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organic acids such as acetic acid, trifluoroacetic acid, formic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid; inorganic bases such as ammonia and hydrazine; and organic bases such as methylamine, ethylamine, hydroxyethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further encompasses hydrates and polymorphs of all of the compounds described herein.

15

The invention further provides pharmaceutical compositions comprising a therapeutically effective amount of any of the compounds described above and a pharmaceutically acceptable carrier. In the subject invention a "therapeutically effective amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes reduction, remission, or regression of the disease. In one embodiment, the therapeutically effective amount is an amount from about 0.01 mg to about 800 mg. In another embodiment, the therapeutically effective amount is an amount from about 0.01 mg to about 500 mg. In another embodiment, the therapeutically effective amount from about 0.01 mg to about 250 mg. In another embodiment, the therapeutically effective amount is an amount from about 0.1 mg to about 60 mg. In another embodiment, the therapeutically effective amount is an amount from about 1 mg to about 20 mg. In one embodiment the

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therapeutically effective amount is an amount from about 0.01 mg per subject per day to about 500 mg per subject per day, preferably from about 0.1 mg per subject per day to about 100 mg per subject per day, e.g., from about 1 mg per subject per day to about 50 mg per subject per day. In the practice of this invention the "pharmaceutically acceptable carrier" is any physiological carrier known to those of ordinary skill in the art as being useful in formulating pharmaceutical compositions.

In one embodiment the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium

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stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

- 5 Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of
10 both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators,
15 stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including
20 monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate.
25 Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.
30
- Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection. Sterile solutions can also be
35 administered intravenously. The compounds may be

-52-

prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.

The invention also provides a method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject any one of the compounds described herein in an amount effective to treat benign prostatic hyperplasia. In a preferred embodiment the compound of the pharmaceutical composition additionally does not cause a fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia. In one preferred embodiment the compound effects treatment of benign prostatic hyperplasia by relaxing lower urinary tract tissue and in particular where lower urinary tract tissue is prostatic smooth muscle.

The invention further provides a method of treating a subject suffering from elevated intraocular pressure which comprises administering to the subject one of the compounds described herein effective to lower intraocular pressure.

The invention further provides a method of treating a subject suffering from a disorder associated with elevated blood cholesterol which comprises administering to the subject one of the compounds described herein effective to inhibit cholesterol synthesis.

The invention also provides a method of treating a

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disease which is susceptible to treatment by antagonism of the α_{1A} receptor which comprises administering to the subject one of the compounds described herein effective to treat the disease.

5

The invention further provides a method of treating a subject suffering from impotency which comprises administering to the subject one of the compounds described herein effective to treat impotency.

10

The invention further provides a method of treating a subject suffering from sympathetically mediated pain which comprises administering to the subject one of the compounds described herein effective to treat sympathetically mediated pain.

15

The invention provides a method of treating a subject suffering from cardiac arrhythmia which comprises administering to the subject one of the compounds described herein effective to treat cardiac arrhythmia.

20

The invention provides a method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject one of the compounds described herein in combination with a 5 alpha-reductase inhibitor effective to treat benign prostatic hyperplasia. In one preferred embodiment the 5-alpha reductase inhibitor is finasteride. The dosage administered to the subject is about 0.01 mg per subject per day to 50 mg per subject per day of finasteride in combination with an α_{1A} antagonist. A more preferred dosage administered to the subject is about 1 mg per subject per day to 7 mg per subject per day of finasteride in combination with an α_{1A} antagonist. The most preferred dosage administered to the subject is

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-54-

about 5 mg per subject per day of finasteride in combination with an α_{1A} antagonist.

5 The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a combination of any of the compounds described herein in combination with finasteride and a pharmaceutically acceptable carrier. In one embodiment the pharmaceutical composition is a therapeutically
10 effective amount of a combination comprising an amount from about 0.01 mg per subject per day to about 500 mg per subject per day of any one of the compounds described herein and an amount of finasteride of about 5 mg per subject per day. A more preferred embodiment of
15 the pharmaceutical composition is a therapeutically effective amount of a combination comprising an amount from about 0.1 mg per subject per day to about 60 mg per subject per day of any one of the compounds described herein and an amount of the finasteride of about 5 mg
20 per subject per day. The most preferred embodiment of the pharmaceutical composition is a therapeutically effective amount of a combination comprising from about 1 mg per subject per day to about 20 mg per subject per day of any one of the compounds described herein and an
25 amount of finasteride of about 5 mg per subject per day.

The invention further provides a method of relaxing lower urinary tract tissue which comprises contacting
30 the lower urinary tract tissue with an amount of one of the compounds described herein effective to relax lower urinary tract tissue. In one embodiment the lower urinary tract tissue is prostatic smooth muscle. In one preferred embodiment the compound additionally does not cause a fall in blood pressure when it is effective to
35 relax lower urinary tract tissue.

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The invention provides a method of relaxing lower urinary tract tissue in a subject which comprises administering to the subject an amount of one of the compounds described herein effective to relax lower urinary tract tissue. In one preferred embodiment the compound does not cause a fall in blood pressure and the lower urinary tract tissue is prostatic smooth muscle.

The invention further provides for a method of inhibiting contraction of prostatic tissue, which comprises administering to the subject an amount of any of the compounds described herein effective to inhibit contraction of prostatic tissue. In one preferred embodiment the prostatic tissue is prostatic smooth muscle and the compound additionally does not cause a fall in blood pressure.

The invention provides for the use of the compounds described herein for the preparation of a pharmaceutical composition for lowering intraocular pressure, inhibiting cholesterol synthesis, and the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be useful. The invention provides for the use of the compounds described herein for the preparation of a pharmaceutical composition for relaxing lower urinary tract tissue and in particular prostatic smooth muscle. The invention further provides for the use of any of compounds described herein for the preparation of a pharmaceutical composition, where the compound additionally does not cause a fall in blood pressure at dosages effective to lower intraocular pressure, to inhibit cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of

-56-

the α_{1A} receptor may be useful.

5 The invention provides for the use of the compounds described herein in the preparation of a medicament for lowering intraocular pressure, inhibiting cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be useful. The invention provides for the use of the
10 compounds described herein in the preparation of a medicament for relaxing lower urinary tract tissue and in particular prostatic smooth muscle. The invention further provides for the use of any of compounds described herein in the preparation of a medicament,
15 where the compound additionally does not cause a fall in blood pressure at dosages effective to lower intraocular pressure, to inhibit cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of
20 the α_{1A} receptor may be useful.

The invention provides a drug which is useful for lowering intraocular pressure, inhibiting cholesterol synthesis, and the treatment of: benign prostatic
25 hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be useful, the effective ingredient of the said drug being any of the compounds described herein. The invention further provides the drug described herein additionally
30 does not cause a fall in blood pressure at dosages effective to lower intraocular pressure, to inhibit cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be
35 useful.

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The invention provides a drug which is useful for relaxing lower urinary tract tissue and in particular prostatic smooth muscle, the effective ingredient of the drug being any of the compounds described herein. The invention further provides a drug which is useful for relaxing lower urinary tract tissue additionally does not cause a fall in blood pressure at dosages effective to relax lower urinary tract tissue.

10 In the preceding methods the compound may be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents, for example, enough saline or glucose to make the solution isotonic, bile salts, acacia, gelatin, 15 sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

The compound may also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration 25 include sterile solutions, emulsions, and suspensions.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of 35 administration.

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In the practice of this invention, the term "lower urinary tract tissue" is used to include prostatic capsule, prostate urethra, and bladder neck.

5

One skilled in the art will readily appreciate that appropriate biological assays will be used to determine the therapeutic potential of the claimed compounds for the treating the above noted disorders.

10

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

15

Experimental Details

Example 1: 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-propyl]-amide (Schemes 5 and 6)

It is a typical procedure for the synthesis of oxazolidinone compounds which are described below.

METHOD A:**a. Amino-(3,4-difluorophenyl)-acetonitrile**

Through a solution of 3,4-difluorobenzaldehyde (25.0 g, 0.18 mol) in MeOH (500 mL) in a round bottom flask, was bubbled ammonia gas for two hours at room temperature. The flask was then cooled to 0°C and trimethylsilyl cyanide (1.3 eq., 0.23 mmol) was then added slowly. The reaction mixture was stirred for 2 h when TLC analysis indicated that the reaction was complete (R_f = 0.35, 3:2 hexane/EtOAc). Solvent was removed in vacuo and the residue was subjected to flash column chromatography on silica gel to obtain 25.0 g (81%) of amino-(3,4-difluorophenyl)-acetonitrile as a yellow syrup.

b. Amino-(3,4-difluorophenyl)-acetic acid methyl ester

To a well stirred solution of amino-(3,4-difluorophenyl)-acetonitrile (22.0 g, 0.130 mol), a solution of HCl in MeOH (200 mL) was added at room temperature. The resulting yellow solution was stirred at room temperature for 10 h and then heated to reflux for 1.5 h. After cooling, the solvent was removed in vacuo and the resulting yellow solid was dissolved in water (200 mL). The aqueous solution was then carefully basified with 20% NaOH solution to pH 9. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was separated and dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to obtain 22.2 g (84%) of amino-(3,4-difluorophenyl)-acetic acid methyl ester as a brownish yellow liquid. It

-60-

was used in the next step without purification.

c. 2-Amino-2-(3,4-difluorophenyl)-ethanol

To a well stirred suspension of LiAlH_4 (4.7 g, 0.125 mol) in THF (120 mL) in a 3-necked round bottom flask fitted with a condenser and a dropping funnel, was added a solution of amino-(3,4-difluorophenyl)-acetic acid methyl ester (10.0 g, 0.05 mol) in THF (100 mL) dropwise at 0°C . The resulting greenish brown suspension was then heated to reflux for 2 h. The reaction mixture was cooled to 0°C and then carefully quenched sequentially with 5 mL of water, 5 mL of 3N NaOH followed by 15 mL of water. The resulting suspension was filtered through a fritted glass funnel. To the residue was added 100 mL Et_2O and the suspension was heated to reflux for 20 min. The suspension was filtered and was combined with the previous filtrate, dried over MgSO_4 , filtered and the solvent was removed in vacuo. 2-amino-2-(3,4-difluorophenyl)-ethanol was obtained as a yellow glassy syrup (8.6 g, 99%) which was used in the next step without further purification.

METHOD B: Synthesis of 2-amino-2-(3,4-difluorophenyl)-ethanol by different route. (Scheme 6)

a. 1-Hydroxy-(3,4-difluorophenyl)-acetophenone

To a solution of KOH (56 g, 1.0 mol) in MeOH (500 mL) was added 3,4-difluoroacetophenone (15.6 g, 0.1 mol) dropwise over 15 min at 0°C . Phenyliodosodiacetate (64.4 g, 0.2 mol) was added in small portions over 20 min period and the resulting yellow-orange solution was stirred overnight at room temperature. The solvent was removed in vacuo to obtain yellow-orange gum. The residue was dissolved in 100 mL of water and 100 mL of brine and was thoroughly extracted with ethyl acetate (3 X 150 mL). The organic layer was dried over Na_2SO_4 and was decanted. The solvent was removed in vacuo to obtain 31.0 g of the acetal as thick yellow oil. It was

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dissolved in 200 mL of acetone and about 10 drops of conc. sulfuric acid. The reaction mixture was stirred at room temperature for 2 h till tlc analysis showed complete consumption of the starting material. The solvent was removed in vacuo and the solid that was obtained was basified by adding sat. NaHCO_3 solution and then it was extracted with ethyl acetate (300 mL). The organic layer was separated and washed with brine. The organic layer was dried over MgSO_4 , filtered and the solvent was removed in vacuo to obtain yellow solid. The yellow solid was washed with cold hexane (to remove iodobenzene impurities) and dried to obtain 11.4 g (66% yield) of 1-hydroxy-(3,4-difluorophenyl)-acetophenone as pale yellow solid. The product was shown to be > 90% pure by NMR and was used in the next step without further purification.

b. 1-Hydroxy-(3,4-difluorophenyl)-acetophenone oxime

To a solution of 1-hydroxy-(3,4-difluorophenyl)-acetophenone (6.0 g, 34.9 mmol) in 150 mL of MeOH was added hydroxylamine hydrochloride (3.16 g, 45.6 mmol) and sodium acetate (9.6 g, 69.6 mmol) at room temperature and the resulting solution was stirred overnight. The solvent was removed and the residue was dissolved in methylene chloride (150 mL) and was washed with 100 mL of sat. NaHCO_3 solution followed by brine. The organic layer was separated and dried over MgSO_4 , filtered and the solvent was removed in vacuo to obtain 1-hydroxy-(3,4-difluorophenyl)-acetophenone-oxime as a yellow solid (5.6 g, 86%). It was used in the next step without any purification.

c. 2-Amino-2-(3,4-difluorophenyl)-ethanol

To a well stirred suspension of LiAlH_4 (3.4 g, 89.5 mmol) in THF (120 mL) in a 3-necked round bottom flask fitted with a condenser and a dropping funnel, was added

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a solution of 1-hydroxy-(3,4-difluorophenyl)-acetophenone-oxime (4.6 g, 24.6 mmol) in THF (50 mL) dropwise at 0°C. The resulting greyish yellow suspension was then heated to reflux for 2 h. The reaction mixture was cooled to 0°C and then carefully quenched sequentially with 3.4 mL of water, 3.4 mL of 3N NaOH followed by 10 mL of water. The resulting suspension was filtered thro' a fritted glass funnel. To the residue was added 100 mL Et₂O and the suspension was heated to reflux for 20 min. The suspension was filtered and was combined with the previous filtrate, dried over MgSO₄, filtered and the solvent was removed in vacuo. 2-Amino-2-(3,4-difluorophenyl)-ethanol was obtained as a yellow glassy syrup (4.1 g, 96%) which was used in the next step without further purification.

d. [1-(3,4-Difluorophenyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester

To a solution of 2-amino-2-(3,4-difluorophenyl)-ethanol (8.6 g, 49.7 mmol) in CHCl₃ (150 mL) at 0°C was added a solution of di-tert-butyl dicarbonate (11.4 g, 52.0 mmol) in CHCl₃ (50 mL) in one portion and the resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (2:1 hexane-EtOAc followed by EtOAc) to obtain [1-(3,4-difluorophenyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester as white solid (10.0 g, 74%).

e. (+)-4-(3,4-Difluorophenyl)-oxazolidin-2-one

To a well stirred suspension of NaH (1.1 g, 45.8 mmol) in THF (40 mL) at room temperature was added a solution of [1-(3,4-difluorophenyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester (5.0 g, 18.3 mmol) in THF 20 mL via a dropping funnel at room temperature. The resulting suspension was stirred for 3 h and then quenched carefully with 10 mL of water. The biphasic

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mixture was extracted with 100 mL of Et₂O, washed with brine, filtered and the solvent was removed in vacuo. The gummy residue thus obtained was purified by column chromatography over silica gel (R_f = 0.15, 3:2 hexane-EtOAc) to obtain (+)-4-(3,4-difluorophenyl)-oxazolidin-2-one as a white flaky solid (2.8 g, 77%). The enantiomers were separated by using Chiralcel OD (4.6 x 250 mm) using 80% hexane/20% isopropyl alcohol/ 0.1 %Diethylamine as the eluting system under isothermal conditions (U.V. 254 nm). The retention times for the two isomers were 16.19 min and 20.08 min respectively. First isomer: $[\alpha]_D = + 62.9$ (c = 0.67, acetone); Anal. Calcd. for C₉H₇NO₂F₂: C, 54.28; H, 3.54; N, 7.03. Found: C, 54.16; H, 3.44; N, 6.96. Second isomer: $[\alpha]_D = - 56.9$ (c = 0.75, acetone); Anal. Calcd. for C₉H₇NO₂F₂: C, 54.28; H, 3.54; N, 7.03. Found: C, 54.31; H, 3.46; N, 6.98. The first isomer was used in the next step.

f. 4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester

To a suspension of NaH (0.14 g, 5.30 mmol) in 20 mL of anhydrous THF under argon, a solution of (+)-4-(3,4-difluorophenyl)-oxazolidin-2-one (0.88 g, 4.42 mmol) in THF was added dropwise via an dropping funnel. The resulting suspension was stirred at room temperature for 30 min. This suspension was then added dropwise via cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (1.11 g, 5.30 mmol) in 25 mL of THF and cooled at -78°C over a period of 15 min. The stirring was continued for 2 h after which the solvent was removed and the residue was purified by column chromatography on silica gel with 1:1 hexane/CH₂Cl₂ followed by CH₂Cl₂ (R_f = 0.4, CH₂Cl₂) to obtain 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester as a white solid (1.55g, 86%).

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g. 3-Amino -propyl-4-pyridyl-piperidine**1-(3-Aminopropyl)-4-[pyrid-2-yl]pyridinium bromide hydrobromide**

Method A: A solution of 2,4'-dipyridyl (5.0 g, 32.0 mmol) and 3-bromopropylamine hydrobromide (7.0 g, 32.0 mmol) in DMF (50.0 mL) and acetonitrile (50.0 mL) was heated at 90-95°C for 1 h. After cooling, the white solid that came out was filtered, washed with Et₂O and dried. The mother liquor was concentrated to remove Et₂O and then heated to 90-95°C for 4 h. The solvent was evaporated and the white residue was triturated with Et₂O (100.0 mL) and filtered. The combined weight of the salt was 11.6 g (97%).

Method B: A well-stirred solution of 2,4'-dipyridyl (12.8 g, 0.08 mol) and N-tert-butoxycarbonyl-3-bromopropylamine (21.3 g, 0.09 mol) in acetonitrile (40.0 mL) was heated to reflux for 6 h. The reaction mixture was cooled to room temperature and filtered. The white solid thus obtained was washed with acetone (2 x 20.0 mL) and chloroform (2 x 20.0 mL) to yield 10.9 g as the first crop. Anal. Calcd. for C₁₃H₁₆N₃Br.HBr.0.5 H₂O: C, 40.65; H, 4.72; N, 10.94. Found: C, 40.83; H, 4.37; N, 11.05.

3-(3',6'-Dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine

To a solution of 1-(3-aminopropyl)-4-[pyrid-2-yl]pyridinium bromide hydrobromide (0.66 g, 1.75 mmol) in 20.0 mL MeOH was added NaBH₄ (0.101 g, 2.62 mmol) in small portions. The reaction mixture was stirred for 30 min and then quenched with 6M HCl solution. The solution was concentrated to 20.0 mL and basified with 50% NaOH solution to pH 12. Extracted with CHCl₃ (5 x 30.0 mL), dried over MgSO₄ and the solvent was removed to give 3-(3',6'-Dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-

propylamine as an oil (0.37 g, 96% yield). It is used in the next step immediately without purification.

3-(3',4',5',6'-Tetrahydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine

5 To a solution of 3-(3',6'-Dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine (3.48 g crude, 15.9 mmol) in MeOH (40 mL), was added 1.0 g of Pearlman's catalyst. The suspension was hydrogenated under 120 psi for 10 h after which the reaction mixture was filtered
10 thro' a pad of celite and the solvent was removed. The residue was purified by column chromatography over silica gel using CH₂Cl₂/methanol/2M NH₃ in MeOH (90:8:4 to 90:40:40) as the eluting system. The product was obtained as a pale yellow oil (3.21 g, 91%).

3-(3',4',5',6'-Tetrahydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine

To a solution of 1-(3-aminopropyl)-4-[pyrid-2-yl]pyridinium bromide hydrobromide (0.53 g) 10.0 mL of 2M NH₃ in MeOH was added PtO₂ (0.1 g) and the reaction
20 mixture was hydrogenated at 110 psi for 6 h and then at 130 psi for 12 h. The catalyst was removed via filtration thro' a pad of celite, washed with MeOH and the solvent was removed. The NMR showed it to be the required product although the accurate weight of the
25 product was not determined due to the presence of ammonium bromide generated during the course of the reaction.

h. (+)-4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'-H-[2,4']bipyridinyl-1'-yl)-propyl]-amide

30 To a solution of 3-amino-propyl-4-pyridyl piperidine (1.1 g, 5.1 mmol) in 100 mL of THF 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (1.55 g, 4.24 mmol) was added and the
35 resulting yellow solution was stirred under argon

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atmosphere for 10 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAc followed by 15% MeOH in EtOAc as the eluting systems (R_f = 0.4, 1:1 MeOH/EtOAc) to obtain a pale yellow glassy oil. It was dissolved in EtOAc (150 mL) and washed thoroughly with 5% KOH solution (4 x 25 mL) in order to remove traces of 4-nitrophenol in the product. The organic layer was separated, washed with brine (25 mL) and then dried over Na_2SO_4 . The solvent was removed and 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-propyl]-amide was obtained as a colorless glassy oil (1.55 g, 82%) which develops some brownish color after 2 h.

To a solution of 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-propyl]-amide (1.53 g, 3.45 mmol) in 10.0 mL of anhydrous EtOH was added a warm solution of 95% fumaric acid (0.48 g, 4.06 mmol) in 8.0 mL EtOH and the resulting solution was kept under a gentle stream of argon for 30 min. Hexane (5 x 1.0 mL) was added over 2 h and the solution was kept under argon atmosphere overnight. Pale yellowish-white small crystals thus obtained were filtered, washed successively with EtOH (10.0 mL) and hexane (10.0 mL). The crystals were pulverized and dried under vacuum at 40°C. The white non-hygroscopic powder (1.6 g, 84%) was found out to be the monofumarate salt after NMR and elemental analysis as shown below. M.P. 142-144°C; $[\alpha]_D = +47.4$ (c = 0.52, MeOH); Anal. Calcd. for $\text{C}_{27}\text{H}_{30}\text{N}_4\text{O}_7\text{F}_2 \cdot \text{H}_2\text{O}$: C, 56.05; H, 5.57; N, 9.68. Found: C, 56.18; H, 5.51; N, 9.54.

Example 2: 4-(3,4-Difluorophenyl)-3-{5-[4-(2-methoxy-

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phenyl)-piperazin-1-yl]-pentyl)-oxazolidin-2-one**a. 4-(3,4-Difluorophenyl)-1-(5-bromopentyl)
oxazolidinone**

5 To a stirred suspension of sodium hydride (203 mg, 8.04 mmol) in THF (5 mL) at 0°C under argon, was added a solution of 4-(3,4-difluorophenyl)oxazolidinone (800 mg, 4.02 mmol) in the mixed solvent of THF (4 mL) and HMPA (0.7 mL, 4.02 mmol) and stirred for 30 min. To this 1,5-dibromopentane (2.17 mL, 16 mmol) was added and the mixture was heated to reflux for 70 min, after which the reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was purified by column chromatography over silica gel with CH₂Cl₂ followed by 5% EtOAc in CH₂Cl₂ as the eluting system (R_f = 0.72, CH₂Cl₂:EtOAc = 3:1) to obtain 4-(3,4-difluorophenyl)-1-(5-bromopentyl) oxazolidinone as a brown liquid (0.70 g, 50%).

b. 4-(3,4-Difluorophenyl)-3-(5-[4-(2-methoxy-phenyl)-piperazin-1-yl]-pentyl)-oxazolidin-2-one

20 To a solution of 4-(3,4-difluorophenyl)-1-(5-bromopentyl) oxazolidinone (60 mg, 0.17 mmol) in 1,6-dioxane (20 mL) at room temperature, were added 1-(2-methoxyphenyl)-piperazine (33.8 mg, 0.17 mmol) and K₂CO₃ (23.8 mg, 0.52 mmol). The resulting mixture was heated to reflux for 12 h after which the reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was dissolved in water and extracted with CH₂Cl₂ (2 X 30 mL), dried over Na₂SO₄. The solvent was then removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAc followed by 5% MeOH in EtOAc as the eluting system (R_f = 0.24, MeOH:EtOAc = 1:8) to obtain 4-(3,4-difluorophenyl)-3-(5-[4-(2-methoxy-phenyl)-piperazin-1-yl]-pentyl)-oxazolidin-2-one as a brown oil (69 mg, 88%). The compound was dissolved in CH₂Cl₂ (3 mL) and

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was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding hydrochloride salt as a yellow solid. M.P. 174-178°C; Anal. Calcd. For $C_{25}H_{33}N_3O_3F_2Cl_2 \cdot 0.65 CH_2Cl_2$: C, 52.43; H, 5.88; N, 7.15. Found: C, 52.12; H, 6.36; N, 6.84.

Example 3: 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(5-bromo-2-methoxy-phenyl)-4-phenyl-piperidin-1-yl]-propyl}-amide

10 a. 4-(5-bromo-2-methoxy)-phenyl-4-phenyl-piperidine hydrochloride

To a 100 mL round bottom flask equipped with a rubber septum and a stirring bar was added 4-hydroxy-4-phenyl-piperidine (5 g, 30.0 mmol) followed by 30 mL of 4-bromoanisole. The resulting solution was stirred at room temperature under argon atmosphere and then $AlCl_3$ (8.0 g, 60.0 mmol) was added in one portion. An exotherm was observed. The reaction mixture was stirred for 8 h (brownish green color), then poured carefully over 600 ml of ice-water and stirred for 10 h. The white suspension was diluted with 100 mL of diethyl ether. The white solid that precipitated out was filtered and washed thoroughly with water (600 mL) followed by diethyl ether (500 mL) to obtain 4-(5-bromo-2-methoxy)-phenyl-4-phenyl-piperidine hydrochloride as a greyish white solid (6.0 g, 52%).

25 b. 3-[4-(5-bromo-2-methoxy)phenyl-4-phenyl-piperidin-1-yl]propylamine

To a solution of 4-(5-bromo-2-methoxy)-phenyl-4-phenyl-piperidine hydrochloride (2.5 g, 6.3 mmol) in 100 mL dioxane was added 3-bromo-N-tert-butoxycarbonyl-propylamine (2.25 g, 9.4 mmol) and K_2CO_3 (3.48 g, 25.2 mmol) and the resulting suspension was heated to reflux for 10 h. The suspension was allowed to cool, filtered

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and the solvent was evaporated to obtain yellow residue which was purified by column chromatography ($R_f = 0.4$, 3:1 EtOAc/MeOH) to obtain 3-[4-(5-bromo-2-methoxy)phenyl-4-phenyl-piperidin-1-yl]-N-tert-butoxycarbonyl-propylamine as a yellow oil (3.15 g). It was dissolved in 35 mL of CH_2Cl_2 and 6.0 mL of trifluoroacetic acid was added with stirring at room temperature under argon atmosphere. After 1 h the solvent was evaporated in vacuo and the residue was basified to pH 10 by adding minimum amount of 1 N KOH solution. The product was extracted with CH_2Cl_2 (3 X 35 mL), dried over MgSO_4 , filtered and the solvent was removed in vacuo to obtain 3-[4-(5-bromo-2-methoxy)phenyl-4-phenyl-piperidin-1-yl]propylamine as a viscous yellow oil (2.26 g, 89% for two steps). It was used in the next step without further purification. The above mentioned steps a and b are representative examples of synthesis of all the 4,4-diaryl piperidine containing side chains described in this document.

c. 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid (3-[4-(5-bromo-2-methoxy-phenyl)-4-phenyl-piperidin-1-yl]-propyl)-amide

To a solution of 3-amino-propyl-4-(5-bromo-2-methoxy)phenyl-4-phenyl piperidine (2.0 g, 4.96 mmol) in 100 mL of THF was added 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (1.81 g, 4.96 mmol) and the resulting yellow solution was stirred under argon atmosphere for 3 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 50% hexane/EtOAc followed by 5% MeOH in EtOAc as the eluting systems ($R_f = 0.4$, 1:3 MeOH/EtOAc) to obtain the product as white foam (wt= 2.2 g). It was dissolved in EtOAc (150 mL) and washed thoroughly with 5% NaOH solution (4 x 25 mL) in order to remove traces of

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4-nitrophenol from the product. The organic layer was separated, washed with brine (25 mL) and then dried over Na_2SO_4 . The solvent was removed after filtration and (+)-1-(3-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carbonyl)-amino-propyl(5-bromo-2-methoxy)phenyl-4-phenyl-piperidine was obtained as a colorless glassy oil (1.84 g, 60%). $[\alpha]_D = +34.3$ ($c = 0.3$, MeOH); The compound was dissolved in CHCl_3 (10 mL) and was treated with 1N HCl in ether (5 mL). The solvent was removed in vacuo to give the corresponding hydrochloride salt as a white solid (2.0 g). M.P. 142-144°C; Anal. Calcd. for $\text{C}_{31}\text{H}_{33}\text{N}_4\text{O}_4\text{BrClF}_2 \cdot 0.3 \text{CHCl}_3$: C, 53.65; H, 4.79; N, 6.00. Found: C, 53.89; H, 4.73; N, 5.74.

Example 4: 1-(3-[(2-Oxo-4-phenyl-[1,3]oxazinane-3-carbonyl)-amino-propyl]-4-phenyl-piperidine-4-carboxylic acid methyl ester (Scheme 7)

a. 3-Amino-3-phenyl-propan-1-ol

To a well stirred suspension of LiAlH_4 (1.3 g, 35.0 mmol) in THF (75 mL) in a round bottom flask fitted with a condenser was added 3-amino-3-phenyl-propionic acid (2.5 g, 15.0 mmol) in small portions at 0°C. The resulting grey suspension was then heated to reflux for 2 h. The reaction mixture was cooled to 0°C and then carefully quenched sequentially with 1.3 mL of water, 1.3 mL of 3N NaOH followed by 4.0 mL of water. The resulting suspension was filtered thro' a fritted glass funnel. To the residue was added 100 mL Et_2O and the suspension was heated to reflux for 20 min. The suspension was filtered and was combined with the previous filtrate, dried over MgSO_4 , filtered and the solvent was removed in vacuo. 3-amino-3-phenyl-propan-1-ol was obtained as a white solid (2.30 g, 100%) which was used in the next step without further purification.

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b. (3-Hydroxy-1-phenyl-propyl)-carbamic acid-tert-butyl ester

To a solution of 3-amino-3-phenyl-propan-1-ol (2.30 g, 15.0 mmol) in CHCl_3 (50 mL) at 0°C was added a solution of di-tert-butyl dicarbonate (3.75 g, 17.1 mmol) in CHCl_3 (25 mL) in one portion and the resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (2:1 hexane-EtOAc followed by EtOAc) to obtain (3-hydroxy-1-phenyl-propyl)-carbamic acid-tert-butyl ester as white solid (4.0 g, 100%).

c. 4-Phenyl-oxazinan-2-one

To a well stirred suspension of 95% NaH (0.24 g, 10.0 mmol) in THF (20 mL) at r.t. was added a solution of (3-hydroxy-1-phenyl-propyl)-carbamic acid-tert-butyl ester (1.0 g, 4.0 mmol) in 10 mL THF via a dropping funnel at room temperature. The resulting suspension was stirred for 3 h and then quenched carefully with 10 mL of water. The biphasic mixture was extracted with 100 mL of Et_2O , washed with brine, filtered and the solvent was removed in vacuo. The gummy residue thus obtained was purified by column chromatography over silica gel ($R_f = 0.2$, 3:2 hexane-EtOAc) to obtain 4-phenyl-oxazinan-2-one as a white flaky solid (0.44 g, 62%).

d. 2-Oxo-4-phenyl-[1,3]-oxazinane-3-carboxylic acid-4-nitro-phenyl ester

To a suspension of NaH (0.07 g, 2.78 mmol) in 10 mL of anhydrous THF under argon, a solution of 4-phenyl-oxazinan-2-one (0.41 g, 2.31 mmol) in THF was added dropwise via an dropping funnel. The resulting suspension was stirred at room temperature for 30 min. This suspension was then added dropwise via cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (0.60 g, 3.0 mmol) in 20 mL of

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THF and cooled at -78°C over a period of 15 min. The stirring was continued for 2 h after which the solvent was removed and the residue was purified by column chromatography on silica gel with 1:1 hexane/ CH_2Cl_2 followed by CH_2Cl_2 ($R_f = 0.4$, CH_2Cl_2) to obtain 2-oxo-4-phenyl-[1,3]-oxazinane-3-carboxylic acid-4-nitro-phenyl ester as a white solid (0.65 g, 82%).

e. 1-{3-[(2-Oxo-4-phenyl-[1,3]oxazinane-3-carbonyl)-amino-propyl]-4-phenyl-piperidine-4-carboxylic acid methyl ester

To a solution of 3-amino-propyl-(4-carbomethoxy-4-phenyl) piperidine (55 mg, 0.20 mmol) in 5 mL of THF, 2-oxo-4-phenyl-[1,3]-oxazinane-3-carboxylic acid-4-nitro-phenyl ester (51 mg, 0.15 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 10 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAC followed by 15% MeOH in EtOAC as the eluting systems ($R_f = 0.4$, 1:1 MeOH/EtOAC) to obtain 2-oxo-4-phenyl-[1,3]-oxazinane-3-carboxylic acid-3-(4-carbomethoxy-4-phenyl)-piperidin-1-yl]-propyl amide as a pale yellow glassy oil (35 mg, 49% yield). It was converted into hydrochloride salt for characterization. Hygroscopic yellow solid.

Anal. Calcd. for $\text{C}_{27}\text{H}_{34}\text{N}_3\text{O}_5\text{Cl} \cdot 2.5 \text{ H}_2\text{O}$: C, 57.80; H, 7.01; N, 7.49. Found: C, 57.98; H, 6.68; N, 6.86.

Example 5: 4-(3,5-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-propyl]-ester

a. 1-(3-hydroxypropyl)-4-[pyrid-2-yl]pyridinium bromide.

A solution of 2,4'-dipyridyl (3.0 g, 18.6 mmol) and 3-bromo-1-propanol (2.02 mL, 22.4 mmol) in acetonitrile (100 mL) was heated to reflux for 2 days. After cooling, the solvent was removed in vacuo and the

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yellow-brown liquid (8.0 g) was directly used for next step without further purification.

b. 3-(3',6'-Dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propanol.

5 To a solution of 1-(3-hydroxypropyl)-4-[pyrid-2-yl]pyridinium bromide (8 g) in 100 mL EtOH was added NaBH₄ (1.41 g, 37.2 mmol) in small portions. The reaction mixture was stirred at room temperature for 12 h and then quenched with drops of water. The solvent was
10 removed in vacuo and the residue was purified by column chromatography over silica gel with 1:4 MeOH/EtOAc followed by 1:4 (2M NH₃ in MeOH) /EtOAc as the eluting system (R_f = 0.6, (2M NH₃ in MeOH) /EtOAc = 1:4) to obtain 3-(3',6'-dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-
15 propanol as an oil (1.58 g, 39% over two steps).

c. 3-hydroxy-propyl-4-pyridyl-piperidine.

To a solution of 3-(3',6'-dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propanol (1.30 g, 5.93 mmol) in mixed solvent (40 mL) of MeOH and 2N HCl (1:1), was
20 added 0.5 g of Pearlman's catalyst. The suspension was hydrogenated under 80 psi at 50°C for 10 h after which the reaction mixture was filtered through a pad of celite and the solvent was removed. The residue was basified by 20% NaOH and extracted by CHCl₃ (7 X 40 ml),
25 dried over Na₂SO₄. The solvent was removed in vacuo to obtain a brown oil (785 mg, 60%).

d. 4-(3,5-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-propyl]-ester

30 To a solution of 4-(3,5-difluorobenzyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (50 mg, 0.137 mmol) in 1,6-dioxane (20 ml) at room temperature, were added 3-hydroxy-propyl-4-pyridyl-piperidine (30 mg, 0.136 mmol) and K₂CO₃ (23.8 mg, 0.52

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mmol). The resulting mixture was heated to reflux for 12 h after which the reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was purified by column chromatography over silica gel with EtOAc followed by 15% MeOH in EtOAc as the eluting system ($R_f = 0.30$, MeOH:EtOAc = 1:1) to obtain 4-(3,5-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-propyl]-ester (20 mg, 33%).

The compound was dissolved in anhydrous EtOH (1 mL) and was treated with a warm solution of 95% fumaric acid (5.3 mg, 0.045 mmol) in EtOH (3 mL). The resulting solution was kept under gentle stream of argon for 30 min after which hexane (2 mL) was added over 1h and the solution was kept under argon overnight. Grey small crystals thus obtained were filtered, washed with EtOH (1 mL) and hexane (1 mL) and dried under vacuum. M.P. 171-173°C; Anal. Calcd. For $C_{27}H_{29}N_3O_8F_2 \cdot 0.27CHCl_3$: C, 55.16; H, 4.97; N, 7.08. Found: C, 55.17; H, 4.98; N, 6.53.

Example 6: 2-Oxo-4-(3,4,5-trifluoro-phenyl)-oxazolidine-3-carboxylic acid[3-[4-(2-carbamoyl-phenyl)-piperazin-1-yl]-propyl]-amide

a. 2-[4-(3-amino-propyl)-piperazin-1-yl]-benzamide

Concentrated sulfuric acid (15 mL) was added to 1-(2-cyanophenyl)piperazine (1.5 g, 8.0 mmol) placed in a round bottom flask and the resulting slurry was stirred at room temperature for 48 h. The reaction mixture was poured on crushed ice very slowly and then basified (pH 9) with 50% solution of NaOH. The aqueous layer was extracted several times with EtOAc, dried over K_2CO_3 , filtered and the solvent was evaporated. 1-(2-carboxamidophenyl)piperazine was obtained as an off-white solid (1.2 g, 73%). It was used in the next step

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without further purification.

b. 2-Oxo-4-(3,4,5-trifluoro-phenyl)-oxazolidine-3-carboxylic acid(3-[4-(2-carbamoyl-phenyl)-piperazin-1-yl]-propyl)-amide

- 5 To a solution of 1-(3-amino-propyl)-4-(2-carboxamido)-phenyl-piperazine (100 mg, 0.38 mmol) in 10 mL of THF, 4-(3,4,5-trifluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (130 mg, 0.34 mmol) was added and the resulting yellow solution was stirred under
10 argon atmosphere for 2 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/EtOAc followed by 1:9 MeOH/EtOAc ($R_f = 0.64$, MeOH/EtOAc=1:3) to obtain (+)-1-{3-{3,4,5-
15 trifluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid(3-[4-(2-carbamoyl-phenyl)-piperazin-1-yl]-propyl)-amide (135 mg, 79%). The compound was dissolved in CH_2Cl_2 (3 mL) and was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding
20 hydrochloride salt as a yellow solid. M. P. 164-168°C; $[\alpha]_D = +50.5$, ($c = 0.28$, MeOH); Anal. Calcd. For $\text{C}_{24}\text{H}_{28}\text{N}_5\text{O}_4\text{F}_3\text{Cl}_2 \cdot 0.25 \text{CHCl}_3$: C, 47.89; H, 4.68; N, 11.51. Found: C, 48.18; H, 5.03; N, 11.14.

- 25 **Example 7: 2-[4-(3-{[4-(3,5-Difluoro-phenyl)-2-oxo-oxazolidine-3-carbonyl]-amino}-propyl)-piperazin-1-yl]-benzoic acid methyl ester** (Schemes 1 and 5)

a. 1-(2-Carbomethoxyphenyl)-piperazine

- 30 To a solution of methyl 2-bromobenzoate (1.63 g, 17.8 mmol) in 1,4-dioxane (100 ml) at room temperature, were added piperazine (15.3 g, 178 mmol) and K_2CO_3 (4.92 g, 35 mmol). The resulting mixture was heated to reflux for 7 days after which the reaction mixture was cooled to room temperature and the solvent and the excess

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piperazine were removed in vacuo and heating with a hot water bath. The residue was dissolved in 1N NaOH solution and extracted with CH_2Cl_2 (6 X 30 ml), dried over Na_2SO_4 . The solvent was removed in vacuo to obtain
5 1-(2-carbomethoxyphenyl)-piperazine as a yellow oil (1.0 g, 26%).

b. 2-[4-(3-([4-(3,5-Difluoro-phenyl)-2-oxo-oxazolidine-3-carbonyl]-amino)-propyl)-piperazin-1-yl]-benzoic acid methyl ester

10 To a solution of 1-(3-amino-propyl)-4-(2-carbomethoxyphenyl)-piperazine (25 mg, 0.090 mmol) in 10 mL of THF, 4-(3,5-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (30 mg, 0.082 mmol) was added and the resulting yellow solution was stirred
15 under argon atmosphere for 2 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/EtOAc followed by 1:9 MeOH/EtOAc ($R_f = 0.75$, MeOH/EtOAc=1:3) to obtain 2-[4-(3-([4-(3,5-difluoro-phenyl)-2-oxo-oxazolidine-3-carbonyl]-amino)-propyl)-
20 piperazin-1-yl]-benzoic acid methyl ester (31 mg, 69%). The compound was dissolved in CH_2Cl_2 (3 mL) and was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding hydrochloride
25 salt as a yellow solid. M. P. 93-96°C; $[\alpha]_D = +45.3$, ($c = 0.29$, MeOH); Anal. Calcd. For $\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_5\text{F}_2\text{Cl}_2 \cdot 0.58 \text{ CH}_2\text{Cl}_2$: C, 50.48; H, 5.16; N, 9.20. Found: C, 50.46; H, 5.56; N, 8.91.

30 **Example 8: 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [4-(4-phenyl-piperidin-1-yl)-butyl]-amide**

To a solution of 1-(4-amino-butyl)-4-phenyl-piperidine (35 mg, 0.151 mmol) in 10 mL of THF, 4-(3,5-

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difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (40 mg, 0.110 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 2 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/EtOAc followed by 1:19 MeOH/EtOAc (R_f = 0.33, MeOH/EtOAc = 1:3) to obtain 4-(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [4-(4-phenyl-piperidin-1-yl)-butyl]-amide (42 mg, 83%). The compound was dissolved in CH_2Cl_2 (3 mL) and was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding hydrochloride salt as a yellow solid. M.P. 80-84°C; Anal. Calcd. For $\text{C}_{25}\text{H}_{30}\text{N}_3\text{O}_3\text{F}_2\text{Cl} \cdot 0.5 \text{CH}_2\text{Cl}_2$: C, 57.09; H, 5.82; N, 7.83. Found: C, 57.08; H, 6.21; N, 7.36.

Example 9: 1-(3-{[5-{3-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carbonyl]-amino}-propyl)-4-phenyl-piperidine-4-carboxylic acid methyl ester (Scheme 8)

a. Hydroxy-(3,4-difluorophenyl)-acetonitrile

To a solution of 3,4-difluorobenzaldehyde (2.86 g, 20.0 mmol) in MeOH (20 mL) in a round bottom flask was added trimethylsilyl cyanide (4.0 mL., 30.0 mmol) at 0°C. The reaction mixture was stirred at room temperature for 10 h when TLC analysis indicated that the reaction was complete (R_f = 0.4, 3:2 hexane/EtOAc). Solvent was removed in vacuo and hydroxy-(3,4-difluorophenyl)-acetonitrile was obtained as a colorless liquid (crude wt. = 3.4 g). It was used in the next step without purification.

b. 2-Amino-1-(3,4-difluorophenyl)-ethanol

To a well stirred solution of hydroxy-(3,4-difluorophenyl)-acetonitrile (3.34 g, 20 mmol), was added a 1.0 M solution of LiAlH_4 in ether (40 mL, 40

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mmol) dropwise at 0°C. The resulting yellow solution was then stirred at room temperature for 2 h. The reaction mixture was cooled to 0°C and then carefully quenched sequentially with 1.5 mL of water, 1.5 mL of 3N NaOH followed by 4.5 mL of water. The resulting suspension was filtered thro' a fritted glass funnel. To the residue was added 100 mL Et₂O and the suspension was heated to reflux for 20 min. The suspension was filtered and was combined with the previous filtrate, dried over MgSO₄, filtered and the solvent was removed in vacuo. 2-amino-1-(3,4-difluorophenyl)-ethanol was obtained as a yellow glassy syrup (3.3 g, 99%) which was used in the next step without further purification.

c. [1-(3,4-Difluorophenyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester

To a solution of 2-amino-1-(3,4-difluorophenyl)-ethanol (3.2 g, 19.8 mmol) in CHCl₃ (15 mL) at 0°C was added a solution of di-tert-butyl dicarbonate (4.36 g, 20.0 mmol) in CHCl₃ (10 mL) in one portion and the resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (2:1 hexane-EtOAc followed by EtOAc) to obtain [2-(3,4-difluorophenyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester as white solid (3.2 g, 59.4%).

d. 5-(3,4-Difluorophenyl)-oxazolidin-2-one

To a well stirred suspension of 95% NaH (0.55 g, 11.8 mmol) in THF (20 mL) at room temperature was added a solution of [2-(3,4-difluorophenyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester (3.2 g, 23.0 mmol) in THF via a dropping funnel at room temperature. The resulting suspension was stirred for 3 h and then quenched carefully with 10 mL of water. The biphasic mixture was extracted with 100 mL of Et₂O, washed with brine, filtered and the solvent was removed in vacuo.

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The gummy residue thus obtained was purified by column chromatography over silica gel (R_f = 0.15, 3:2 hexane-EtOAc) to obtain 5-(3,4-difluoro-phenyl)-oxazolidin-2-one as a white solid (1.1 g, 47%).

5 **e. 5-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester**

To a suspension of 95% NaH (0.08 g, 3.0 mmol) in 5.0 mL of anhydrous THF under argon, a solution of 5-(3,4-difluorophenyl)-oxazolidin-2-one (0.5 g, 2.51 mmol) in 10 5.0 mL THF was added dropwise via an dropping funnel. The resulting suspension was stirred at room temperature for 30 min. This suspension was then added dropwise via cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (0.07 g, 3.26 15 mmol) in 20 mL of THF, cooled at -78°C , over a period of 15 min. The stirring was continued for 2 h after which the solvent was removed and the residue was purified by column chromatography on silica gel with 1:1 hexane/ CH_2Cl_2 followed by CH_2Cl_2 (R_f = 0.4, CH_2Cl_2) to 20 obtain 5-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester as a white solid (0.7 g, 76%).

25 **f. 1-(3-([5-(3-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carbonyl]-amino)-propyl)-4-phenyl-piperidine-4-carboxylic acid methyl ester**

To a solution of 3-amino-propyl-4-carbomethoxy-4-phenyl piperidine (0.04 g, 0.13 mmol) in 10 mL of THF 5-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.04 g, 0.10 mmol) was added and the 30 resulting yellow solution was stirred under argon atmosphere for 10 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAc followed by 15% MeOH in EtOAc as the eluting systems (R_f 35 = 0.4, 1:1 MeOH/EtOAc) to obtain 1-(3-([5-(3-(3,4-

difluorophenyl)-2-oxo-oxazolidine-3-carbonyl]-amino}-propyl)-4-phenyl-piperidine-4-carboxylic acid methyl ester as a pale yellow glassy oil (0.03 g, 60%). It was converted into its hydrochloride salt. M.P. = 121-125°C; Anal. Calcd. for $C_{26}H_{30}N_3O_4F_2Cl_2 \cdot 0.2 H_2O$: C, 57.66; H, 5.66; N, 7.76. Found: C, 57.80; H, 6.15; N, 7.95.

Example 10: 4-(3-Chloro-4-fluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(4,4-diphenyl-piperidin-1-yl)-propyl]-amide (Schemes 2 and 5)

To a solution of 3-amino-propyl-4,4-diphenyl piperidine (0.04 g, 0.1 mmol) in 5 mL of THF was added 4-(3-chloro-4-fluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.04 g, 0.12 mmol) and the resulting yellow solution was stirred under argon atmosphere for 3 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 50% hexane/EtOAC followed by 5% MeOH in EtOAC as the eluting systems (R_f = 0.45, 1:3 MeOH/EtOAC) to obtain 4-(3-Chloro-4-fluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(4,4-diphenyl-piperidin-1-yl)-propyl]-amide as white foam (wt = 0.03 g). It was converted into its hydrochloride salt. M.P. 112-115°C; Anal. Calcd. for $C_{30}H_{32}N_3O_3Cl_2F \cdot 0.5 CHCl_3$: C, 57.95; H, 5.18; N, 6.65. Found: C, 58.06; H, 5.74; N, 6.30.

Example 11: 4-(3,4-Difluoro-phenyl)-2-thioxo-oxazolidine-3-carboxylic acid [3-(4-o-toluy1-4-p-toluy1-piperidin-1-yl)-propyl]-amide (Scheme 9)

a. 4-(3,4-Difluorophenyl)-oxazolidine-2-thione

To a solution of 2-amino-2-(3,4-difluorophenyl)-ethanol (600 mg, 3.46 mmol) in CH_2Cl_2 (20 ml) at room temperature, was added 1,1'-thiocarbonyldiimidazole (755

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mg, 3.81 mmol). The resulting solution was heated by a pre-heated oil-bath (110°C) to reflux for 10 h after which the reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was purified by column chromatography over silica gel with CH₂Cl₂ as the eluting system (R_f = 0.68, CH₂Cl₂:EtOAc = 3:1) to obtain 4-(3,4-difluorophenyl)-oxazolidine-2-thione a brown oil (290 mg, 39%).

b. 4-(3,4-Difluorophenyl)-2-thione-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester.

To a suspension of NaH (41 mg, 1.62 mmol) in 20 mL of anhydrous THF under argon, a solution of 4-(3,4-difluorophenyl)-oxazolidine-2-thione (290 mg, 1.35 mmol) in THF was added dropwise via a dropping funnel. The resulting suspension was stirred at room temperature for 30 min. This suspension was then added dropwise via cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (336 mg, 1.62 mmol) in 20 mL of THF and cooled at -78°C over a period of 15 min. The stirring was continued for 2 h after which the solvent was removed and the residue was purified by column chromatography on silica gel with 1:1 hexane/CH₂Cl₂, then 3:7 hexane/CH₂Cl₂, followed by CH₂Cl₂ (R_f = 0.50) to obtain 4-(3,4-difluorophenyl)-2-thione-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester as a yellow solid (130 mg, 25%).

c. 4-(3,4-Difluoro-phenyl)-2-thioxo-oxazolidine-3-carboxylic acid [3-(4-o-toluy1-4-p-toluy1-piperidin-1-yl)-propyl]-amide

To a solution of 1-(3-amino-propyl)-4-(4-methyl)-phenyl-4-(2-methyl)-phenyl-piperidine (60 mg, 0.186 mmol) in 10 mL of THF, 4-(3,4-Difluorophenyl)-2-thione-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (30 mg, 0.079 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 2 h at room temperature. The

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solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/EtOAc followed by 1:19 MeOH/EtOAc (R_f = 0.66, MeOH/EtOAc=1:3) to obtain 4-(3,4-Difluoro-phenyl)-2-thioxo-oxazolidine-3-carboxylic acid [3-(4-o-toluyyl-4-p-toluyyl-piperidin-1-yl)-propyl]-amide (16 mg, 36%). The compound was dissolved in CH_2Cl_2 (3 mL) and was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding hydrochloride salt as a yellow solid. M.P.= 132-136°C; Anal. Calcd. for $\text{C}_{32}\text{H}_{36}\text{N}_3\text{O}_2\text{SCl} \cdot 0.60 \text{ CH}_2\text{Cl}_2$: C, 60.14; H, 5.76; N, 6.45. Found: C, 59.97; H, 6.14; N, 6.12.

Example 12: 4-phenyl-2-thioxo-thiazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-propyl]-amide (Scheme 9)

a. 4-(S)-Phenyl-thiazolidine-2-thione

To a solution of (S)-(+)-2-Phenylglycinol (1.40 g, 10 mmol) in 1N KOH/ H_2O (10 ml) at room temperature, was added carbon disulfide (3 ml, 50 mmol). The resulting solution was heated by a pre-heated oil-bath (110°C) to reflux for 20 h after which the reaction mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 X 30 ml), dried over Na_2SO_4 . The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/ CH_2Cl_2 , followed by CH_2Cl_2 as the eluting system (R_f = 0.09, CH_2Cl_2 :hexane = 7:3) to obtain 4(S)-phenyl-thiazolidine-2-thione (170 mg, 9%).

b. 4-(S)-Phenyl-2-thione-thiazolidine-3-carboxylic acid-4-nitro-phenyl ester.

To a suspension of NaH (26 mg, 1.04 mmol) in 10 mL of anhydrous THF under argon, a solution of 4(S)-Phenyl-

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thiazolidine-2-thione (170 mg, 0.87 mmol) in THF was added dropwise via an dropping funnel. The resulting suspension was stirred at room temperature for 30 min. This suspension was then added dropwise via cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (217 mg, 1.04 mmol) in 20 mL of THF and cooled at -78°C over a period of 15 min. The stirring was continued for 2 h after which the solvent was removed and the residue was purified by column chromatography on silica gel with 1:1 hexane/CH₂Cl₂, then 3:7 hexane/CH₂Cl₂ followed by CH₂Cl₂ (R_f= 0.50) to obtain (+)-4(S)-phenyl-2-thione-thiazolidine-3-carboxylic acid-4-nitro-phenyl ester as a pale yellow solid (200 mg, 64%).

c. 4-phenyl-2-thioxo-thiazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'H-[2,4']biphenyl-1'-yl)-propyl]-amide

To a solution of 3-amino-propyl-4-pyridyl-piperidine (35 mg, 0.159 mmol) in 10 mL of THF, (+)-4(S)-Phenyl-2-thione-thiazolidine-3-carboxylic acid-4-nitro-phenyl ester (50 mg, 0.139 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 2 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/EtOAc followed by 1:9 MeOH/EtOAc (R_f= 0.21, MeOH/EtOAc=1:3) to obtain 4-(3,4-Difluoro-phenyl)-2-thioxo-thiazolidine-3-carboxylic acid [3-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-propyl]-amide (10 mg, 14%). The compound was dissolved in CH₂Cl₂ (3 mL) and was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding hydrochloride salt as a yellow solid.

M.P.= 67-70°C; Anal. Calcd. for C₂₃H₃₁N₄OS₂Cl₂·0.67 CHCl₃: C, 47.82; H, 5.37; N, 9.42. Found: C, 47.85; H, 6.12; N,

6.52.

Example 13: (-)-2-Oxo-8,8a-dihydro-3aH-1-(S)-oxa-3-(R)-
aza-cyclopent[1]indene-3-carboxylic acid-[3-(1-4-cyano-
4-phenyl-piperidin-1-yl)-propyl-amide (Scheme 10)

a. Synthesis of (+)-3,3a,8,8a-tetrahydro-1(S)-oxa-3(R)-
aza-cyclopenta[a]inden-2-one

To a solution of (1R,2S)-(+)-cis-1-amino-2-indanol (1.0 g, 6.7 mmol) in 30 ml methylene chloride in 100-ml round bottom flask equipped with a stirring bar, was added 1,1'-carbonyldimidazole (1.20 g, 7.4 mmol) at room temperature. The resulting solution was heated by a pre-heated oil-bath (110°C) to reflux for 10 h after which the reaction mixture was cooled to room temperature and the formation of white crystal was observed. The white crystal was filtered off, washed with minimum CH₂Cl₂ (2 mL) and then dried in vacuo. (+)-3,3a,8,8a-Tetrahydro-1(S)-oxa-3(R)-aza-cyclopenta[a]inden-2-one was obtained as a white crystal (500 mg, 43%). $[\alpha]_D = -71.1$ (c = 0.28, acetone). M.P. 203-204°C. Anal. Calcd. for C₁₀H₉NO₂: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.44; H, 5.12; N, 7.98.

b. 2-Oxo-1,3a,8,8a-tetrahydro-2H-3-aza-
cyclopenta[a]indene-3-carboxylic acid 4-nitro-phenyl
ester.

To a suspension of NaH (73 mg, 2.88 mmol) in 20 mL of anhydrous THF under argon, a solution of 3,3a,8,8a-tetrahydro-1(R)-oxa-3(S)-aza-cyclopenta[a]inden-2-one (420 mg, 2.40 mmol) in THF was added dropwise via an dropping funnel. The resulting suspension was stirred at room temperature for 30 min. This suspension was then added dropwise via cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (598 mg, 2.88 mmol) in 25 mL of

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THF and cooled at -78°C over a period of 15 min. The stirring was continued for 2 h after which the solvent was removed and the residue was purified by column chromatography on silica gel with 4:1 hexane/EtOAc followed by 3:2 hexane/EtOAc ($R_f = 0.51$, hexane/EtOAc=1:1) to obtain a white solid (680 mg, 83%).

c. (-)-2-Oxo-8,8a-dihydro-3aH-1-(S)-oxa-3-(R)-aza-cyclopent[1]indene-3-carboxylic acid-[3-(1-4-cyano-4-phenyl-piperidin-1-yl)-propyl-amide

To a solution of 1-(3-amino-propyl)-4-cyano-4-phenyl-piperidine (25 mg, 0.103 mmol) in 10 mL of THF, 2-Oxo-1,3a,8,8a-tetrahydro-2H-3-aza-cyclopenta[a]indene-3-carboxylic acid 4-nitro-phenyl ester (40 mg, 0.118 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 2 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/EtOAc followed by EtOAc ($R_f = 0.35$) to obtain (-)-2-Oxo-8,8a-dihydro-3aH-1-(S)-oxa-3-(R)-aza-cyclopent[1]indene-3-carboxylic acid-[3-(1-4-cyano-4-phenyl-piperidin-1-yl)-propyl-amide] (19 mg, 35%). The compound was dissolved in CH_2Cl_2 (3 mL) and was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding hydrochloride salt as a white solid. M. P. $98-102^{\circ}\text{C}$; $[\alpha]_D = -96.5$, ($c = 0.21$, MeOH); Anal. Calcd. For $\text{C}_{26}\text{H}_{29}\text{N}_4\text{O}_3\text{Cl} \cdot 0.48 \text{ CH}_2\text{Cl}_2$: C, 60.96; H, 5.79; N, 10.74. Found: C, 60.94; H, 6.69; N, 8.02.

Example 14: 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[2-methyl-4-(2-nitro-phenyl)-piperazin-1-yl]-propyl}-amide

a. (S)-(+)-3-methyl-1-(2-nitrophenyl)-piperazine

To a solution of 2-bromo-nitrobenzene (0.6 g, 3.0 mmol)

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in 1,4-dioxane (15 mL) was added (S)-(+)-2-methylpiperazine (0.5 g, 0.5 mmol) and powdered K_2CO_3 (15.0 mmol, 1.5 g) and the resulting suspension was heated at reflux for 10 h. After the suspension was cooled, it was filtered through a sintered glass funnel and the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield (S)-(+)-3-methyl-1-(2-nitrophenyl)-piperazine as an orange oil (0.53 g, 80%). It was converted into (S)-(+)-3-methyl-1-(2-nitrophenyl)-4-(3-aminopropyl)-piperazine by the usual procedure.

b. 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[2-methyl-4-(2-nitro-phenyl)-piperazin-1-yl]-propyl}-amide

To a solution of (S)-(+)-3-methyl-1-(2-nitrophenyl)-4-(3-aminopropyl)-piperazine (35 mg, 0.126 mmol) in 10 mL of THF, 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (50 mg, 0.137 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 2 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/EtOAc followed by MeOH:EtOAc=1:9 (R_f = 0.58, MeOH:EtOAc=1:3) to obtain 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[2-methyl-4-(2-nitro-phenyl)-piperazin-1-yl]-propyl}-amide (55 mg, 87%). The compound was dissolved in CH_2Cl_2 (3 mL) and was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding hydrochloride salt as a pale yellow solid. M. P. 115-119°C; $[\alpha]_D = +38.3$, ($c = 0.22$, CH_2Cl_2); Anal. Calcd. For $C_{24}H_{28}N_5O_5F_2Cl \cdot 0.72 C_6H_{12}$: C, 56.50; H, 6.38; N, 11.63. Found: C, 56.63; H, 6.35; N, 10.08.

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Example 15: 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid (3-[4-methyl-4-phenyl-piperidin-1-yl]-propyl)-amide

a. 1-Benzyl-4-methyl-4-piperidinol

5 To a solution of 1-benzyl-4-piperidone (5.6 mL, 30.0 mmol) in 50 mL THF was added a solution of methyllithium in THF (24.0 mL, 36 mmol) dropwise at 0°C over 15 min. The reaction mixture was allowed to warm to room temperature over 3 h and then quenched with 30 mL of
10 sat. NH_4Cl solution. The organic layer was extracted with diethyl ether (2 X 100 mL) and the combined organic layer was washed with brine (100 mL). The organic layer was separated, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to obtain yellow gum. It
15 was purified by column chromatography over silica gel with 9:1 EtOAc-MeOH as the eluting system to obtain 1-benzyl-4-methyl-4-piperidinol as a yellow thick oil (3.6 g, 59% yield).

b. 1-Benzyl-4-methyl-4-phenyl piperidine

20 To a solution of 1-benzyl-4-methyl-4-piperidinol (3.6 g, 17.5 mmol) in 75 mL of benzene was added AlCl_3 (11.7 g, 87.7 mmol) in one portion at room temperature. After stirring at room temperature for 30 min, the reaction mixture was heated to reflux for 8 h. The red colored
25 solution was allowed to cool and then poured over 100 g of ice-water. It was extracted with EtOAc (2 X 100 mL) and the organic layer was washed with solution of Rochelle's salt. The organic layer was separated, dried over Na_2SO_4 , filtered and the solvent was removed in
30 vacuo to obtain 1-benzyl-4-methyl-4-phenyl piperidine as a red oil (4.5 g, 97% yield). It was used in the next step without further purification.

c. 4-Methyl-4-phenyl piperidine

To a cooled suspension of 10% Pd-C (0.5 g) in 10 mL

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methanol was added a solution of 1-benzyl-4-methyl-4-phenyl piperidine (4.5 g, 17.0 mmol) in 40 mL of methanol and the resulting suspension was hydrogenated in a Parr bomb under 250 psi of hydrogen for two days. The suspension was filtered through a pad of celite and the solvent was removed from the filtrate to obtain 4-methyl-4-phenyl piperidine as a yellow solid (3.3 g, 99% yield).

d. 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-methyl-4-phenyl-piperidin-1-yl]-propyl}-amide

To a solution of 1-(3-amino-propyl)-4-methyl-4-phenyl-piperidine (60 mg, 0.258 mmol) in 10 mL of THF, 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (60 mg, 0.165 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 2 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/EtOAc followed by MeOH:EtOAc=1:19 (R_f = 0.45, MeOH:EtOAc=1:3) to obtain 4-(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-methyl-4-phenyl-piperidin-1-yl]-propyl}-amide (56 mg, 74%). The compound was dissolved in CH_2Cl_2 (3 mL) and was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding hydrochloride salt as a pale yellow solid. M. P. 176-178°C; $[\alpha]_D = +76.9$, ($c = 0.23$, MeOH); Anal. Calcd. For $\text{C}_{25}\text{H}_{30}\text{N}_3\text{O}_3\text{F}_2\text{Cl} \cdot 0.60 \text{ CH}_2\text{Cl}_2$: C, 56.32; H, 5.94; N, 7.70. Found: C, 56.30; H, 5.80; N, 7.35.

Example 16: 4-(3,4-Difluorophenyl)-4-methyl-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(2-methylphenyl)-4-(4-methylphenyl)-piperidin-1-yl]-propyl}amide (Scheme 11)

a. 2-(3,4-Difluorophenyl)propan-2-ol

To a solution of ethylmagnesium bromide in ether (38.0 mL, 38.0 mmol) at 0°C, was added a solution of 3',4'-difluoroacetophenone (5.0 g, 32.0 mmol) in diethyl ether (35mL). The reaction mixture was stirred at 0°C for 1 h when TLC analysis indicated that the reaction was complete (R_f = 0.3, 3:1 hexane/EtOAc). The reaction was quenched carefully by adding 38 mL of water. It was extracted with diethyl ether (2 X 30 mL), washed with Rochelle's salt followed by brine and the organic layer was dried over Na_2SO_4 . The solvent was removed in vacuo after filtration and 2-(3,4-difluorophenyl)propan-2-ol was obtained as a colorless oil (crude wt. = 5.4 g, 97%) which looked > 90% pure by NMR. It was used in the next step without purification.

b. 1,2-Difluoro-4-isopropenyl-benzene

To a solution of 2-(3,4-difluorophenyl)propan-2-ol (1.0 g, 5.8 mmol) in 40 mL benzene was added 0.1 g of p-toluenesulfonic acid and the solution was heated to 60°C. TLC analysis showed disappearance of the starting material. After cooling, the solution was extracted with EtOAc, washed with saturated NaHCO_3 , dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. 1,2-difluoro-4-isopropenyl-benzene was obtained as a yellow oil (0.82 g, 92% yield).

c. 2-(3,4-Difluorophenyl)-2-methyl-oxirane

To a biphasic solution of 1,2-difluoro-4-isopropenyl-benzene (0.81 g, 5.1 mmol) in CH_2Cl_2 (50 mL) and 50 mL of phosphate buffer (made by dissolving 0.3 g of NaHPO_4 and 0.35 g of NaH_2PO_4 in 50 mL water, pH = 8) at 0°C, was added a solution of 3-chloroperoxybenzoic acid (approx. 75% solid, 3.32 g, 10.2 mmol) via a dropping funnel fitted with a cotton plug dropwise in two batches. The solution was stirred at room temperature overnight. It was extracted with CH_2Cl_2 , washed with

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sat. $\text{Na}_2\text{S}_2\text{O}_4$ solution followed by water. The organic layer was finally washed with sat. NaHCO_3 , separated, dried over Na_2SO_4 , filtered and solvent was removed in vacuo. 2-(3,4-Difluorophenyl)-2-methyl-oxirane was
5 obtained as a pale yellow oil (0.65 g, 74% yield). It was used in the next step without purification.

d. 1-Amino-2-(3,4-difluorophenyl)-propan-2-ol and 2-Amino-2-(3,4-difluorophenyl)-propan-1-ol

To a solution of 2-(3,4-difluorophenyl)-2-methyl-oxirane
10 (1.2 g, 7.06 mmol) in 10 mL of acetonitrile was added sodium azide (0.69g, 10.6 mmol) followed by lithium perchlorate (1.13 g, 10.6 mmol) and the suspension was heated to reflux overnight. After cooling, it was
15 extraced with EtOAc, washed with saturated NaHCO_3 , dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. The light brown oil that was obtained was a 10:1 mixture of 1-azido-2-(3,4-difluorophenyl)-propan-2-ol and 2-azido-2-(3,4-difluorophenyl)-propan-1-ol (crude wt
20 2.0 g). It was dissolved in 40 mL of diethyl ether, cooled to 0°C and then treated with a solution of lithium aluminum hydride (20.0 mL, 20 mmol). The resulting yellow suspension was then stirred at room temperature for 2 h. The reaction mixture was cooled to
25 0°C and then carefully quenched sequentially with 0.8 mL of water, 0.8 mL of 3N NaOH followed by 2.5 mL of water. The resulting suspension was filtered thro' a fritted glass funnel. To the residue was added 100 mL Et_2O and the suspension was heated to reflux for 20 min. The suspension was filtered and was combined with the
30 previous filtrate, dried over MgSO_4 , filtered and the solvent was removed in vacuo. 1-Amino-2-(3,4-difluorophenyl)-propan-2-ol and 2-amino-2-(3,4-difluorophenyl)-propan-1-ol was obtained as a yellow glassy syrup (1.16 g, 87%) which was used in the next

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step immediately without further purification.

e. [2-(3,4-Difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester and [1-(3,4-Difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester

5 To a solution of 1-amino-2-(3,4-difluorophenyl)-propan-2-ol and 2-amino-2-(3,4-difluorophenyl)-propan-1-ol (1.2 g, 6.4 mmol) in CHCl_3 (50 mL) at 0°C was added a solution of di-tert-butyl dicarbonate (1.74 g, 7.9 mmol) in CHCl_3 (10 mL) in one portion and the resulting
10 solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (2:1 hexane-EtOAc followed by EtOAc) to obtain [2-(3,4-difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester and [1-(3,4-Difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester as a white solid
15 (1.1 g, 60.1%).

f. 5-(3,4-Difluorophenyl)-5-methyl-oxazolidin-2-one and 4-(3,4-Difluorophenyl)-4-methyl-oxazolidin-2-one

20 To a well stirred solution of [2-(3,4-difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester and [1-(3,4-Difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester (1.1 g, 3.8 mmol) THF (50 mL) was added 95% NaH (0.23 g, 9.6 mmol) at room temperature. The
25 resulting suspension was heated to reflux for 1 h and then stirred at room temperature overnight. It was quenched carefully with ice. The biphasic mixture was extracted with 100 mL of EtOAc, washed with brine, dried over Na_2SO_4 , filtered and the solvent was removed in
30 vacuo. The two diastereomers were separated by column chromatography over silica gel. The first diastereomer that came out was 4-(3,4-difluorophenyl)-4-methyl-oxazolidin-2-one (0.05 g, $R_f = 0.3$, 3:2 hexane-EtOAc) and the second isomer was 5-(3,4-difluorophenyl)-5-

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methyl-oxazolidin-2-one (0.61 g, R_f = 0.2, 3:2 hexane-EtOAc).

g. 4-(3,4-Difluorophenyl)-4-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester

5 To a a solution of 4-(3,4-Difluorophenyl)-4-methyl-oxazolidin-2-one (0.05 g, 0.23 mmol) in 5.0 mL THF was added 95% NaH (0.01 g, 0.28 mmol) in one portion. The resulting suspension was stirred at room temperature for 20 min. This suspension was then added dropwise via a
10 syringe into another round bottom flask containing a solution of 4-nitrophenylchloroformate (0.06 g, 0.28 mmol) in 5 mL of THF, cooled at -78°C , over a period of 15 min. The stirring was continued for 1 h after which the solvent was removed and the residue was purified by
15 column chromatography on silica gel with 3:2 hexane/EtOAc (R_f = 0.5) to obtain 4-(3,4-difluorophenyl)-4-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester as a white solid (0.06 g, 69%).

h. 5-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester

20 To a a solution of 4-(3,4-Difluorophenyl)-4-methyl-oxazolidin-2-one (0.61 g, 2.86 mmol) in 20 mL THF was added 95% NaH (0.07 g, 3.0 mmol) in one portion. The resulting suspension was stirred at room temperature for 20 min. This suspension was then added dropwise via a
25 cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (0.62 g, 3.1 mmol) in 20 mL of THF, cooled at -78°C , over a period of 15 min. The stirring was continued for 1 h after which
30 the solvent was removed and the residue was purified by column chromatography on silica gel with 3:2 hexane/EtOAc (R_f = 0.6) to obtain 4-(3,4-difluorophenyl)-4-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester as a white solid (0.7 g, 67%).

i. 4-(3,4-Difluorophenyl)-4-methyl-2-oxo-oxazolidine-3-

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carboxylic acid (3-[4-(2-methylphenyl)-4-(4-methylphenyl)-piperidin-1-yl]-propyl)amide

To a solution of 3-amino-propyl-4-(2-methyl)phenyl-4-(4-methyl)phenyl-piperidine (0.09 g, 0.27 mmol) in 10 mL of THF, 4-(3,4-Difluorophenyl)-4-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.06 g, 0.15 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 10 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAC followed by 15% MeOH in EtOAC as the eluting systems (R_f = 0.3, 1:3 MeOH/EtOAC) to obtain 4-(3,4-difluorophenyl)-4-methyl-2-oxo-oxazolidine-3-carbonyl)-amino-propyl}-4-(2-methyl)phenyl-4-(4-methyl)phenyl-piperidine as a pale yellow glassy oil (0.06 g, 73%) as a viscous oil. It was converted into its hydrochloride salt. M.P. = 98-101°C; Anal. Calcd. for $C_{33}H_{38}N_3O_3F_2Cl \cdot 1.0 CH_2Cl_2$: C, 59.79; H, 5.90; N, 6.15. Found: C, 59.40; H, 5.99; N, 5.92.

Example 17: 5-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid (3-[4-(2-methoxy-5-methyl)phenyl-4-(4-methylphenyl)-piperidin-1-yl]propyl)amide (Scheme 11)

To a solution of 3-amino-propyl-4-(2-methoxy-5-methyl)phenyl-4-(4-methyl)phenyl-piperidine (0.09 g, 0.27 mmol) in 10 mL of THF, 5-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.04 g, 0.11 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 10 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAC followed by 15% MeOH in EtOAC as the eluting systems (R_f

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= 0.3, 1:3 MeOH/EtOAc) to obtain 4-(3,4-difluorophenyl)-4-methyl-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(2-methoxy-5-methyl)phenyl-4-(4-methylphenyl)-piperidin-1-yl]propyl}amide as a pale yellow glassy oil (0.06 g, 85%) as a viscous oil. It was converted into its hydrochloride salt. M.P. = 82-85°C; Anal. Calcd. for $C_{34}H_{40}N_3O_4F_2Cl \cdot 0.7 CH_2Cl_2$: C, 60.61; H, 6.07; N, 6.11. Found: C, 60.73; H, 6.46; N, 6.12.

Example 18: *cis* (+)-4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid{3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl}amide (Scheme 12)

a. 1-(3,4-Difluorophenyl)propan-1-ol

To a solution of 3,4-difluorobenzaldehyde (5.0 g, 35.2 mmol) in diethyl ether (35 mL) in a round bottom flask was added a solution of ethylmagnesium bromide in THF (38.0 mL, 38.0 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1 h when TLC analysis indicated that the reaction was complete (R_f = 0.5, 8:1 hexane/EtOAc). The reaction was quenched carefully by adding 38 mL of water. It was extracted with diethyl ether (2 X 30 mL), washed with brine and the organic layer was dried over Na_2SO_4 . The solvent was removed in vacuo after filtration and 1-(3,4-difluorophenyl)propan-1-ol was obtained as a yellow oil (crude wt. = 6.0 g) which looked > 90% pure by NMR. It was used in the next step without purification.

b. 1-(3,4-Difluorophenyl)propan-1-one

In a round bottom flask containing pyridinium chlorochromate (12.5 g, 58.1 mmol) was added celite 545 (25 g) and with the help of a magnetic stirrer the solids were mixed together. 200 mL of CH_2Cl_2 was added followed by a solution of 1-(3,4-difluoro-phenyl)propan-1-ol (5.0 g, 29.1 mmol) in 10 mL of CH_2Cl_2 and the

resulting brown suspension was stirred overnight at room temperature. The suspension was filtered through a sintered glass funnel and the solvent was removed in vacuo from the pale green colored filtrate. The green oil was then diluted with diethyl ether (200 mL) and it was filtered through a pad of celite to remove the metal impurities. The solvent was removed in vacuo to obtain 1-(3,4-difluorophenyl)propan-1-one as a pale yellow oil (3.4 g, 69% yield). It was used in the next step without purification.

c. 1-(3,4-Difluorophenyl)-2-hydroxy-propan-1-one

In a round bottom flask containing 200 mL of MeOH was added pellets of potassium hydroxide (23.0 g, 410.0 mmol). The solution was cooled to 0°C and 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one (7.0 g, 41.2 mmol) in 10 mL MeOH was added dropwise. The solution was stirred for 10 min and then iodobenzene diacetate (22.5 g, 70 mmol) was added in two portions. The solution first became orange and then turned yellow. It was stirred overnight at room temperature and then solvent was removed in vacuo. The residue was dissolved in water and was extracted with ethyl acetate (3 X 100 mL). The combined organic extracts were washed with brine and then dried over Na₂SO₄. After filtration, the solvent was removed in vacuo to get 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one dimethyl acetal as a yellow viscous oil (crude wt. = 9.2 g). It was dissolved in 150 mL of acetone and 10 drops of concentrated sulfuric acid were added. After stirring for 3 h, TLC analysis indicated that the reaction was complete. Acetone was removed in vacuo and after basification with saturated NaHCO₃, the residue was extracted in EtOAc and was washed with brine. The organic layer was separated, dried over Na₂SO₄ and then filtered. The solvent was removed in vacuo and the

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residue was purified by silica gel chromatography (R_f = 0.4, 3:2 hexane/EtOAc) to obtain 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one as a pale yellow oil (3.3 g, 51% yield over two steps).

5 **d. 1-(3,4-Difluorophenyl)-2-hydroxy-propan-1-one-oxime**

To a well stirred solution of 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one (5.5 g, 29.6 mmol) in MeOH (200 mL) was added hydroxylamine hydrochloride (2.6 g, 38.4 mmol) and sodium acetate (8.1 g, 59.2 mmol) and the the turbid
10 solution was stirred overnight at room temperature. The solvent was evaporated and the residue was extracted with CH_2Cl_2 . The organic layer was washed with sat. NaHCO_3 , separated, dried over Na_2SO_4 and then filtered. The solvent was removed in vacuo to obtain 1-(3,4-
15 difluorophenyl)-2-hydroxy-propan-1-one-oxime as an orangish yellow oil (5.8 g, 97%). It was used in the next step without purification.

e. 1-Amino-1-(3,4-difluorophenyl)-propan-2-ol

To a well stirred solution of 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one-oxime (5.8 g, 28.4 mmol), was added
20 a 1.0 M solution of LiAlH_4 in ether (90 mL, 90 mmol) dropwise at 0°C . The resulting yellow solution was then stirred at room temperature for 2 h. The reaction mixture was cooled to 0°C and then carefully quenched
25 sequentially with 3.5 mL of water, 3.5 mL of 3N NaOH followed by 10.5 mL of water. The resulting suspension was filtered thro' a fritted glass funnel. To the residue was added 100 mL Et_2O and the suspension was heated to reflux for 20 min. The suspension was
30 filtered and was combined with the previous filtrate, dried over MgSO_4 , filtered and the solvent was removed in vacuo. 1-amino-1-(3,4-difluorophenyl)-propan-2-ol was obtained as a yellow glassy syrup (3.6 g, 66%) which was used in the next step without further purification.

35 **f. [1-(3,4-Difluorophenyl)-2-hydroxy-propyl]-carbamic**

acid-tert-butyl ester

To a solution of 1-amino-1-(3,4-difluorophenyl)-propan-2-ol (3.5 g, 19.1 mmol) in CHCl_3 (15 mL) at 0°C was added a solution of di-tert-butyl dicarbonate (5.1 g, 23.6 mmol) in CHCl_3 (10 mL) in one portion and the resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (2:1 hexane-EtOAc followed by EtOAc) to obtain [1-(3,4-difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester as a viscous oil (3.3 g, 60.2%).

g. 4-(3,4-Difluorophenyl)-5-methyl-oxazolidin-2-one

To a well stirred solution of [1-(3,4-difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester (0.43 g, 1.5 mmol) THF (20 mL) was added 95% NaH (0.09 g, 3.8 mmol) at room temperature. The resulting suspension was stirred for 3 h at about 35°C (warm water bath) and then quenched carefully with ice. The biphasic mixture was extracted with 100 mL of EtOAc, washed with brine, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. The two diastereomers were separated by column chromatography over silica gel (First isomer: 0.11 g, $R_f = 0.6$, 3:1 hexane-EtOAc; second isomer: 0.23 g, $R_f = 0.5$, 3:1 hexane-EtOAc). NOE experiment suggested that the first diastereomer had the methyl and the aryl group in trans configuration while the second diastereomer had cis relationship between the two groups.

Enantiomers of each of these diastereoisomers were separated by HPLC by using Chiralcel OD (4.6 x 250 mm) using 80% hexane/20% isopropyl alcohol/ 0.1% diethylamine as the eluting system (12 mL/min) under isothermal conditions (U.V. 254 nm). The retention times for the two isomers of the trans-oxazolidinone were 12.1 min $\{[\alpha]_D = +36.4$ ($c = 0.25$, acetone)} and 15.6 min $\{[\alpha]_D = -30.8$ ($c = 0.20$, acetone)},

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respectively. The retention times for the two isomers of the *cis*-oxazolidinone were 13.7 min ($[\alpha]_D = + 65.8$ ($c = 0.92$, acetone)) and 19.9 min ($[\alpha]_D = - 65.8$ ($c = 0.74$, acetone)) respectively. The next steps may be performed on each of the four enantiomers individually in the following manner, which describes the synthesis of the *cis* (+) enantiomer.

h. 4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester

To a suspension of 95% NaH (0.01 g, 0.38 mmol) in 5.0 mL of anhydrous THF under argon, a solution of 4-(3,4-difluorophenyl)-5-methyl-oxazolidin-2-one (0.07 g, 0.33 mmol) in 5.0 mL THF was added dropwise via a syringe. The resulting suspension was stirred at room temperature for 20 min. This suspension was then added dropwise via a syringe into another round bottom flask containing a solution of 4-nitrophenylchloroformate (0.08 g, 0.4 mmol) in 10 mL of THF, cooled at -78°C , over a period of 15 min. The stirring was continued for 1 h after which the solvent was removed and the residue was purified by column chromatography on silica gel with 1:1 hexane/ CH_2Cl_2 , followed by CH_2Cl_2 ($R_f = 0.4$, CH_2Cl_2) to obtain 4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester as a white solid (0.07 g, 56%).

i. 3-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-propylamine

To a solution of 4-fluorophenylmagnesium bromide (110.0 mmol, 55.0 mL of 2.0 M solution) in 150.0 mL THF at 0°C was added 1-benzyl-4-piperidone (55.0 mmol, 10.2 mL) dropwise. The resulting solution was stirred under argon atmosphere for 1.5 h and then quenched with 100.0 mL of saturated NH_4Cl solution. The organic layer was

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separated and the aqueous layer was extracted with 100.0 mL of Et₂O. The combined organic extracts were washed with brine, separated and dried over Na₂SO₄. The solution was filtered and the solvent was removed in vacuo to obtain a yellow oil which was purified by passing through a silica gel column with 4:1 hexane/EtOAc followed by 1:1 hexane/EtOAc as the eluting system. 1-Benzyl-4-(4-fluoro-phenyl)-piperidin-4-ol was obtained as a pale yellow oil in 89% yield (13.9 g). It was dissolved in 150.0 mL of toluene and p-toluenesulfonic acid monohydrate (50.0 mmol, 9.5 g) was added. The resulting suspension was heated to reflux for 8 h. After the suspension was cooled, it was basified with 3 N NaOH solution and was extracted with Et₂O (2 X 50 mL). The organic extracts were combined, washed with brine and the organic layer was dried over Na₂SO₄. The solvent was removed in vacuo to obtain 1-benzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine as a yellow viscous oil (12.0 g, 92% yield) which was used in the next step without further purification.

To a solution of 1-benzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine (45.0 mmol, 12.0 g) in 100 mL MeOH was added 1.0 g of Pd(OH)₂ and the resulting suspension was hydrogenated under 200 psi of H₂ in a stainless steel bomb for two days. The suspension was passed through a pad of celite and the filtrate was concentrated in vacuo to obtain 4-(4-fluoro)-phenyl-piperidine (7.5 g, 94%) as a viscous oil. It was converted into 3-[4-(4-fluoro-phenyl)-piperidin-1-yl]-propylamine by the route described previously in Example 1.

j. *cis* (+)-(4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid(3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl)amide

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To a solution of 3-amino-propyl-4-(4-fluoro)phenyl-piperidine (0.04 g, 0.12 mmol) in 10 mL of THF (+)-4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.03 g, 0.08 mmol) (made from the (+)-enantiomer from HPLC of the *cis* diastereomer separated by column chromatography) was added and the resulting yellow solution was stirred under argon atmosphere for 10 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAC followed by 15% MeOH in EtOAC as the eluting systems ($R_f = 0.4$, 1:3 MeOH/EtOAC) to obtain (+)-4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid(3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl)amide as a pale yellow glassy oil (0.03 g, 66%). It was converted into its hydrochloride salt. M. P. 108-112°C; $[\alpha]_D = +56.7$, ($c = 0.20$, MeOH); Anal. Calcd. For $C_{25}H_{29}N_3O_3F_3Cl \cdot 0.36 CH_2Cl_2$: C, 56.14; H, 5.52; N, 7.75. Found: C, 56.17; H, 5.90; N, 7.20.

Example 19: *trans* (+)-4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid(3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl)amide (Scheme 12)

In an analogous manner as described above for Example 18, Steps h-j, the *trans* (+)-4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.03 g, 0.08 mmol) (made from the (+)-enantiomer from HPLC of the *trans* diastereomer separated by column chromatography) was converted into *trans* (+)-4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid(3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl)amide in 70% yield. It was converted into hydrochloride salt.

M.P. = 80-83°C (shrinks around 58°C); $[\alpha]_D = +27.4$ ($c =$

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0.49, MeOH); Anal. Calcd. for $C_{25}H_{29}N_3O_3F_3Cl \cdot 1.0 H_2O$: C, 56.55; H 6.07; N 7.91 Found: C, 56.49; H, 5.88; N 7.80.

Example 20: 4-(3,4-Difluoro-benzyl)-2-oxo-oxazolidine-3-carboxylic acid (3-[4-(2-carbamoylphenyl)-piperazin-1-yl]-propyl)amide

a. 2-Amino-3-(3,4-difluoro)-phenyl-propan-1-ol

To a well stirred suspension of $LiAlH_4$ (0.48 g, 12.5 mmol) in THF (30 mL) in a round bottom flask fitted with a condenser was added 3,4-difluorophenyl alanine (1.0 g, 5.0 mmol) in small portions at 0°C. The resulting grey suspension was then heated to reflux for 2 h. The reaction mixture was cooled to 0°C and then carefully quenched sequentially with 0.5 mL of water, 0.5 mL of 3N NaOH followed by 1.5 mL of water. The resulting suspension was filtered through a fritted glass funnel. To the residue was added 50 mL Et_2O and the suspension was heated to reflux for 20 min. The suspension was filtered and was combined with the previous filtrate, dried over $MgSO_4$, filtered and the solvent was removed in vacuo. 2-Amino-3-(3,4-difluoro)-phenyl-propan-1-ol was obtained as a white solid (0.5 g, 100%) which was used in the next step without further purification.

b. (+)-[1-(3,4-Difluorobenzyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester

To a solution of 2-amino-3-(3,4-difluoro)-phenyl-propan-1-ol (0.5 g, 2.62 mmol) in $CHCl_3$ (20 mL) at 0°C was added a solution of di-tert-butyl dicarbonate (0.64 g, 2.90 mmol) in $CHCl_3$ (10 mL) in one portion and the resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (2:1 hexane-EtOAc followed by EtOAc) to obtain (+)-[1-(3,4-difluorobenzyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester as white solid (0.64 g, 99%).

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c. (+)-4-(3,4-Difluoro-benzyl)-oxazolidin-2-one

To a well stirred suspension of 95% NaH (0.12 g, 5.0 mmol) in THF (20 mL) at r.t. was added a solution of (+)-[1-(3,4-difluorobenzyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester (1.0 g, 4.0 mmol) in 10 mL THF via a dropping funnel at room temperature. The resulting suspension was stirred for 3 h and then quenched carefully with 10 mL of water. The biphasic mixture was extracted with 50 mL of Et₂O, washed with brine, filtered and the solvent was removed in vacuo. The gummy residue thus obtained was purified by column chromatography over silica gel (R_f = 0.25, 3:2 hexane-EtOAc) to obtain (+)-4-(3,4-difluoro-benzyl)-oxazolidin-2-one as a white solid (0.32 g, 76%).

d. (+)-4-(3,4-Difluoro-benzyl)-oxazolidin-2-one-3-carboxylic acid-4-nitro-phenyl ester

To a suspension of NaH (0.03 g, 1.30 mmol) in 10 mL of anhydrous THF under argon, a solution of (+)-4-(3,4-difluoro-benzyl)-oxazolidin-2-one (0.21 g, 1.0 mmol) in 10 mL THF was added dropwise via an dropping funnel. The resulting suspension was stirred at room temperature for 30 min. This suspension was then added dropwise via cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (0.30 g, 1.5 mmol) in 20 mL of THF and cooled at -78°C over a period of 15 min. The stirring was continued for 2 h after which the solvent was removed and the residue was purified by column chromatography on silica gel with 1:1 hexane/CH₂Cl₂ followed by CH₂Cl₂ (R_f = 0.4, CH₂Cl₂) to obtain (+)-4-(3,4-difluoro-benzyl)-oxazolidin-2-one-3-carboxylic acid-4-nitro-phenyl ester as a yellow solid (0.35 g, 82%).

e. 4-(3,4-Difluoro-benzyl)-2-oxo-oxazolidine-3-carboxylic acid (3-[4-(2-carbamoylphenyl)-piperazin-1-yl]-propyl)amide

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To a solution of 1-(3-amino-propyl)-4-(2-carboxamido)-phenyl-piperazine (30 mg, 0.114 mmol) in 10 mL of THF, 4-(3,4-difluorobenzyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (30 mg, 0.079 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 2 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 1:1 hexane/EtOAc followed by 1:19 MeOH/EtOAc (R_f = 0.70, MeOH/EtOAc=1:3) to obtain 4-(3,4-Difluoro-benzyl)-2-oxo-oxazolidine-3-carboxylic acid (3-[4-(2-carbamoylphenyl)-piperazin-1-yl]-propyl)amide (20 mg, 44%). The compound was dissolved in CH_2Cl_2 (3 mL) and was treated with 1N HCl in ether (1 mL). The solvent was removed in vacuo to give the corresponding hydrochloride salt as a yellow solid. M. P. 82-85°C; $[\alpha]_D = +34.3$, (c = 0.49, MeOH); Anal. Calcd. For $\text{C}_{25}\text{H}_{31}\text{N}_5\text{O}_4\text{F}_2\text{Cl}_2 \cdot 3.5 \text{ H}_2\text{O}$: C, 47.10; H, 6.01; N, 10.99. Found: C, 47.12; H, 5.94; N, 10.94.

20

Example 21: 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid(2-[4-phenylpiperidine-4-(carboxylic acid methyl ester)]ethyl)amide (Scheme 5)

To a solution of 2-amino-ethyl-4-carbomethoxy-4-phenyl piperidine (0.03 g, 0.12 mmol) in 5 mL of THF was added 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.04 g, 0.10 mmol) and the resulting yellow solution was stirred under argon atmosphere for 3 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 50% hexane/EtOAc followed by 5% MeOH in EtOAc as the eluting systems (R_f = 0.5, 1:3 MeOH/EtOAc) to obtain the product as colorless oil (wt= 0.02 g). The compound was converted

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into its hydrochloride salt. M.P. 80-85°C; $[\alpha]_D = +51.6$, ($c = 0.11$, MeOH); Anal. Calcd. for $C_{25}H_{28}N_3O_5ClF_2 \cdot 0.5 CHCl_3$: C, 52.48; H, 4.92; N, 7.20. Found: C, 52.54; H, 5.13; N, 7.27.

5

Example 22: 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid{3-[4-(4-fluoro-2-methyl-phenyl)-piperidin-1-yl]-propyl} amide

a. 1-Benzyl-4-(5-fluoro-2-methyl)-phenyl-4-piperidinol

10 To a cooled solution of n-BuLi (6.0 mL, 15.0 mmol) in 20 mL THF was added 2-Bromo-5-fluoro toluene (1.9 mL, 15.0 mmol) dropwise at -78°C over 15 min. The reaction mixture was allowed to warm to 0°C over 1 h and then cooled to -78°C. 1-Benzyl-4-piperidone (1.48 mL, 8.0 mmol) was added the white slurry and the reaction mixture was warmed to 0°C over 2 h. The reaction was then quenched with 10 mL of sat. NH_4Cl solution. The organic layer was extracted with diethyl ether (2 X 50 mL) and the combined organic layer was washed with brine (100 mL). The organic layer was separated, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to obtain yellow oil. It was purified by column chromatography over silica gel with 3:2 hexane-EtOAc as the eluting system to obtain 1-benzyl-4-(5-fluoro-2-methyl)-phenyl-4-piperidinol as a yellow thick oil (1.1 g, 46% yield).

b. 1-Benzyl-4-(4-Fluoro-2-methyl)-phenyl-1,2,3,6-tetrahydropyridine

30 To a solution of 1-benzyl-4-(5-fluoro-2-methyl)-phenyl-4-piperidinol (1.1 g, 3.68 mmol) in 100 mL toluene was added p-toluenesulfonic acid monohydrate (1.39 g, 7.35 mmol) and the resulting solution was heated to reflux for 8 h. The suspension was cooled and the basified with 10% KOH solution and extracted with EtOAc (2 X 50 mL).
35 The organic layer was washed with brine (30 mL). The

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organic layer was separated, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to obtain 1-benzyl-4-(4-Fluoro-2-methyl)-phenyl-1,2,3,6-tetrahydropyridine as a pale yellow oil (0.9 g, 87% yield). It was used in the next step without further purification.

c. 3-amino-propyl-4-(4-fluoro-2-methyl)phenyl-piperidine

To a cooled suspension of 10% Pd-C (0.1 g) in 10 mL methanol was added a solution of 1-benzyl-4-(4-Fluoro-2-methyl)-phenyl-1,2,3,6-tetrahydropyridine (0.9 g, 3.2 mmol) in 20 mL of methanol and the resulting suspension was hydrogenated at room temperature under 1 atm of hydrogen for 10 h. The suspension was filtered through a pad of celite and the solvent was removed from the filtrate to obtain 4-(4-fluoro-2-methyl)-phenyl-piperidine which was converted into its hydrochloride salt (0.62 g, 99% yield). It was used in the next step without further purification. It was converted into 3-amino-propyl-4-(4-fluoro-2-methyl)phenyl-piperidine by the usual procedure.

d. 4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid{3-[4-(4-fluoro-2-methyl-phenyl)-piperidin-1-yl]-propyl}amide

To a solution of 3-amino-propyl-4-(4-fluoro-2-methyl)phenyl-piperidine (0.03 g, 0.11 mmol) in 5 mL of THF was added 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.04 g, 0.10 mmol) and the resulting yellow solution was stirred under argon atmosphere for 8 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with 50% hexane/EtOAC followed by 5% MeOH in EtOAC as the eluting systems (R_f = 0.4, 1:3 MeOH/EtOAC) to obtain the product as colorless oil (wt= 0.02 g). The compound was converted into its hydrochloride salt. Off-white solid. M.P. = 60-64°C; $[\alpha]_D^{25}$ = + 36.6 (c = 0.15, MeOH); Anal.

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Calcd. for $C_{25}H_{29}N_3O_3F_3Cl \cdot 0.25 CHCl_3$: C, 55.97; H, 5.44; N, 7.76. Found: C, 55.91; H, 5.66; N, 7.87.

Preparation of Side Chains.

5 **1. 3-(4,4-Diphenylpiperidin-1-yl)propylamine.**

a. 4,4-Diphenylpiperidine hydrochloride. A mixture of 4-piperidone monohydrate hydrochloride (15.0 g, 0.0976 mol) and $AlCl_3$ (130 g, 0.976 mol, 10.0 eq) in anhydrous benzene (600 mL) were stirred at reflux for 4 hours.

10 The mixture was cooled to room temperature, poured into ice (300 g) and water (50 mL), and filtered. The solid was washed with toluene and dried to afford 19.2 g (72%) of an off-white solid, which was characterized spectroscopically.

15 **b. 3-(4,4-Diphenylpiperidin-1-yl)propionitrile.** To a suspension of 4,4-diphenylpiperidine hydrochloride (0.195 g, 0.712 mmol) in EtOH (1.5 mL) was added Et_3N (0.25 mL, 1.8 mmol, 2.6 eq) followed by acrylonitrile (0.13 mL, 2.01 mmol, 2.8 eq). The resulting solution
20 was stirred at room temperature under argon for 15 min and then concentrated. Water was added, and the mixture was extracted with EtOAc (3 X 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give 170 mg (87%) of a tan solid, which was
25 characterized spectroscopically and used in the next reaction without purification.

c. 3-(4,4-Diphenylpiperidin-1-yl)propylamine. To a stirred solution of 3-(4,4-diphenylpiperidin-1-yl)propionitrile (2.00 g, 6.89 mmol) in anhydrous THF
30 (20 mL) under argon was added a solution of BH_3 in THF (1.0 M, 24.1 mL, 24 mmol, 3.5 eq) at room temperature. The mixture was refluxed for 4.5 hours and then cooled to room temperature. Aqueous HCl (6 N, 50 mL) was added and stirring was continued for 1 hour. The mixture was

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basified to pH 9 by addition of 6 N aq. NaOH, extracted with CH_2Cl_2 (3 X 10 mL), dried (MgSO_4) and concentrated. The residue was purified by flash chromatography (SiO_2 , EtOAc-MeOH-isopropylamine 9:1:0 to 4:1:0.2) to give 1.35 g (66%) of tan solid, which was characterized spectroscopically.

2. 3-(4-Cyano-4-phenylpiperidin-1-yl)propylamine.

a. 3-(4-Cyano-4-phenylpiperidin-1-yl)propylphthalimide.

A mixture of 4-cyano-4-phenylpiperidine hydrochloride (111 g, 0.5 mol), 3-bromopropylphthalimide (135.39 g, 0.505 mol), potassium carbonate (276.42 g, 2 mol), and potassium iodide (5.4 g) in DMF (1 L) was stirred and heated at 100-110 °C for 8 h. About 80% of the solvent was evaporated at reduced pressure, the residue was diluted with dichloromethane (1 L) and washed with brine (3 X 300 mL) and dried (Na_2SO_4). Solvent was evaporated from the dichloromethane solution and the residue was treated with isopropanol (400 mL) and cooled. The pale yellow crystalline product formed was filtered, washed with ice-cold isopropanol and dried (168.6 g, 90%); M.p. 96-98 °C.

b. 3-(4-Cyano-4-phenylpiperidin-1-yl)propylamine.

To a solution of 3-(4-cyano-4-phenylpiperidin-1-yl)propylphthalimide (112 g, 0.3 mol) in methanol (1.5 L), hydrazine (30 mL) was added and the mixture was stirred and refluxed for 20 h. It was cooled, the white solid formed was filtered and washed with more methanol (200 mL). Solvent was evaporated from the filtrate and residue was dried under vacuum for 4 h. Chloroform (500 mL) was added to this, stirred for 1 h and filtered. The white solid was washed with more chloroform (200 mL), the solvent was evaporated from the combined filtrates to leave the product as an oil (70 g, 96%).

3. 3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine.

a. 4-Methoxycarbonyl-4-phenylpiperidine. To a stirred solution of H_2SO_4 (16 mL) in MeOH (400 mL), 4-phenyl-4-piperidinecarboxylic acid 4-methylbenzenesulfonate (37.7 g, 0.1 mole) was added and the mixture was stirred and refluxed for 8 hours. Excess methanol was evaporated at reduced pressure and the residue was poured into a mixture of ice and 6 N NaOH. The pH was adjusted to 10-11 by adding more 6 N NaOH and extracted with CH_2Cl_2 (3 X 150 mL). The combined CH_2Cl_2 extracts were dried (MgSO_4) and the solvent evaporated to leave the desired product as a viscous oil. The product (20.2 g, 92%) was used without further purification.

b. 3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine.

A mixture of 4-methoxycarbonyl-4-phenylpiperidine (8.5 g, 0.039 mol), 3-bromopropylamine hydrobromide (12.7 g, 0.058 mol), potassium carbonate (13.475 g, 0.0957 mole), and KI (3.24 g, 0.0195 mol) in 1,4-dioxane (200 mL) was stirred and refluxed for 24 hours. Dioxane was evaporated at reduced pressure, the residue was treated with ice-cold 6 N NaOH (400 mL) and extracted with CH_2Cl_2 (4 X 120 mL). Solvent was evaporated from the combined dried (K_2CO_3) extracts and the residue was purified by column chromatography on silica gel using $\text{CHCl}_3/\text{MeOH}/2 \text{ M NH}_3$ in MeOH (20:2:1) as the eluent to afford the product as a viscous oil (7.8 g, 72%).

4. 3-Aminopropyl-4-pyridyl-piperidine

a. 1-(3-Aminopropyl)-4-[pyrid-2-yl]pyridinium bromide hydrobromide.

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A solution of 2,4'-dipyridyl (5.0 g, 32.0 mmol) and 3-bromopropylamine hydrobromide (7.0 g, 32.0 mmol) in DMF (50.0 mL) and acetonitrile (50.0 mL) was heated at 90-95 °C for 1 h. After cooling, the white solid that came out was filtered, washed with Et₂O and dried. The mother liquor was concentrated to remove Et₂O and then heated at 90-95°C for 4 h. The solvent was evaporated and the white residue was triturated with Et₂O (100.0 mL) and filtered. The combined weight of the salt was 11.6 g (97%).

b. 3-(3',6'-Dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine.

To a solution of 1-(3-aminopropyl)-4-[pyrid-2-yl]pyridinium bromide hydrobromide (0.66 g, 1.75 mmol) in 20.0 mL MeOH was added NaBH₄ (0.101 g, 2.62 mmol) in small portions. The reaction mixture was stirred for 30 min and then quenched with 6M HCl solution. The solution was concentrated to 20.0 mL and basified with 50% NaOH solution to pH 12. Extracted with CHCl₃ (5 x 30.0 mL), dried over MgSO₄ and the solvent was removed to give 3-(3',6'-dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine as an oil (0.37 g, 96% yield). It is used in the next step immediately without purification.

c. 3-Aminopropyl-4-(2-pyridyl)piperidine.

To a solution of 3-(3',6'-dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine (3.48 g crude, 15.9 mmol) in MeOH (40 mL), was added 1.0 g of Pearlman's catalyst. The suspension was hydrogenated under 120 psi for 10 h after which the reaction mixture was filtered through a pad of celite and the solvent was removed. The residue was purified by column chromatography over silica gel using CH₂Cl₂/methanol/2M NH₃ in MeOH (90:8:4 to 90:40:40) as the eluting system. The product was obtained as a pale yellow oil (3.21 g, 91%).

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5. 3-(4-Acetoxy-4-phenylpiperidin-1-yl)propylamine.**a. N-Benzyloxycarbonyl-3-(4-hydroxy-4-phenylpiperidin-1-yl)propylamine.**

A mixture of 4-hydroxy-4-phenylpiperidine (5 g, 0.0282 mol), N-benzyloxycarbonyl-3-bromopropylamine (8.445 g, 0.031 mol), and potassium carbonate (7.795 g, 0.0564 mole) in acetone (200 mL) was stirred and refluxed for 12 hours. Acetone was evaporated at reduced pressure, the residue was treated with ice-cold water (400 mL) and extracted with CH₂Cl₂ (4 X 120 mL). Solvent was evaporated from the combined dried (sodium sulfate) extracts and the residue was found to be almost pure desired product (9.5 g, 91%) by tlc and ¹H-NMR and was used as such without any further purification.

b. N-Benzyloxycarbonyl-3-(4-acetoxy-4-phenylpiperidin-1-yl)propylamine.

To a solution of N-benzyloxycarbonyl-3-(4-hydroxy-4-phenylpiperidin-1-yl)propylamine (0.5 g, 1.36 mmol) in THF (20 mL) at 0 °C, sodium hydride (60% suspension in paraffin, 65 mg, 1.63 mmol, 1.2 eq.) was added and the mixture was stirred for 1.5 h. To this acetyl bromide (0.12 mL, 1.63 mmol) was injected and the mixture was stirred at 0 °C for 30 minutes and at room temperature for 3 h. Solvent was evaporated, the residue was mixed with dichloromethane (100 mL), and washed with water (2 X 20 mL). Solvent was evaporated from the dried dichloromethane solution gave the product as a viscous oil (0.485 g, 87%). The ¹H-NMR showed this product to be pure and was used in the next step without any further purification.

c. 3-(4-Acetoxy-4-phenylpiperidin-1-yl)propylamine.

A mixture of N-benzyloxycarbonyl-3-(4-acetoxy-4-phenylpiperidin-1-yl)propylamine (3.0 g, 7.3 mmol) and 10% Pd-C (0.3 g) in 1M ammonia in

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methanol (50 mL) was hydrogenated at 70 psi at room temperature for 4 h. The catalyst was removed by filtration and the solvent was evaporated to leave the product as a viscous oil (2.01 g, 99%), the ¹H-NMR showed it to be very pure and was used in the next step without any purification.

6. 3-(4-Cyano-4-phenylpiperidin-1-yl)-2-hydroxypropylamine.

10 a. 3-(4-Cyano-4-phenylpiperidin-1-yl)(2-hydroxypropyl)phthalimide

A mixture of 4-cyano-4-phenylpiperidine (10.0 g, 45 mmol) and 2,3-epoxypropylphthalimide (10.94 g, 54 mmol) in DMF (100 mL) was stirred and heated at 70 °C for 72 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (1000/28/14) as the eluent, to obtain the desired product as a viscous oil (16.45 g, 86%).

20 b. 3-(4-Cyano-4-phenylpiperidin-1-yl)-2-hydroxypropylamine.

A mixture of 3-(4-cyano-4-phenylpiperidin-1-yl)-(2-hydroxypropyl)phthalimide (10 g, 23.48 mmol) and hydrazine (6.01 g, 188 mmol, 8 eq.) in methanol (100 mL) was stirred and refluxed for 4.5 h. It was cooled, filtered, and the solid was washed with methanol (30 mL). Evaporation of solvent from the filtrate gave the product as a viscous oil (5.53 g, 94%).

30 7. 3-(4-Cyano-4-phenylpiperidin-1-yl)-2-fluoropropylamine.

a. 3-(4-Cyano-4-phenylpiperidin-1-yl)(2-fluoropropyl)phthalimide

A mixture of 3-(4-cyano-4-phenylpiperidin-1-yl)-(2-hydroxypropyl)phthalimide (2.60 g, 6.1 mmol) and

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diethylaminosulfur trifluoride (DAST, 1.96 g, 12.2 mmol) in benzene (100 mL) was stirred and heated at 70 °C under argon atmosphere for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (1000/28/14) as the eluent, to obtain the desired product as a viscous oil (1.30 g, 50%).

b. 3-(4-Cyano-4-phenylpiperidin-1-yl)-2-fluoropropylamine.

A mixture of 3-(4-cyano-4-phenylpiperidin-1-yl)-(2-fluoropropyl)phthalimide (3.80 g, 8.88 mmol) and hydrazine (2.27 g, 71.04 mmol, 8 eq.) in methanol (100 mL) was stirred and refluxed for 4.5 h. It was cooled, filtered, and the solid was washed with methanol (30 mL). Evaporation of solvent from the filtrate gave the product as a viscous oil (1.9 g, 85%).

8. 3-[4-(2-Pyridyl)-piperidin-1-yl]-3-methylpropylamine.

a. 3-[4-(2-Pyridyl)-piperidin-1-yl]-2-methylpropionitrile. A mixture of 4-(2-pyridyl)-piperidine (1.56 g, 10 mmol) and crotononitrile (1.34 g, 20 mmol, 2 eq) in ethanol (100 mL) was stirred and refluxed for 16 h and the solvent and excess crotononitrile were evaporated under vacuum. The residue was purified by column chromatography on silica gel using dichloromethane-methanol-2M ammonia in methanol (45/4/2) as the eluent to give the desired product as a viscous oil (2.09 g, 94%), which got solidified on standing.

b. 3-[4-(2-Pyridyl)-piperidin-1-yl]-3-methylpropylamine. To a stirred solution of 3-[4-(2-pyridyl)-piperidin-1-yl]-3-methylpropionitrile (0.446 g, 2 mmol) in anhydrous THF (10 mL) under argon was added a solution of BH₃ in

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THF (1.0 M, 10 mL, 10 mmol, 5 eq) at room temperature. The mixture was refluxed for 4.5 hours and then cooled to room temperature. Aqueous HCl (6 N, 50 mL) was added and stirring was continued for 1 hour. The mixture was
5 basified to pH 9 by addition of 6 N aq. NaOH, extracted with CH₂Cl₂ (3 X 10 mL), dried (potassium carbonate) and the solvent evaporated to leave the product as a viscous oil (0.42 g, 93%) the ¹H-NMR of it showed it to be pure enough to use it in the next step.

10

9. 3-[4-(2-Pyridyl)-piperidin-1-yl]-2-methylpropylamine.

a. 3-[4-(2-Pyridyl)-piperidin-1-yl]-2-

methylpropionitrile. A mixture of 4-(2-pyridyl)-
15 piperidine (3.12 g, 20 mmol) and 1-methylacrylonitrile (5 mL) in methanol (100 mL) was stirred and refluxed for 48 h and the solvent and excess 1-

methylacrylonitrile were evaporated under vacuum. The residue was purified by column chromatography on silica gel using dichloromethane-methanol-2M ammonia in
20 methanol (45/4/2) as the eluent to give the desired product as a viscous oil (3.30 g, 74%), which got solidified on standing.

b. 3-[4-(2-Pyridyl)-piperidin-1-yl]-2-methylpropylamine.

To a stirred solution of 3-[4-(2-pyridyl)-piperidin-1-
25 yl]-2-methylpropionitrile (0.446 g, 2 mmol) in anhydrous THF (10 mL) under argon was added a solution of BH₃ in THF (1.0 M, 10 mL, 10 mmol, 5 eq) at room temperature. The mixture was refluxed for 4.5 hours and then cooled to room temperature. Aqueous HCl (6 N, 50 mL) was added
30 and stirring was continued for 1 hour. The mixture was basified to pH 9 by addition of 6 N aq. NaOH, extracted with CH₂Cl₂ (3 X 10 mL), dried (potassium carbonate) and the solvent evaporated to leave the product as a viscous oil (0.436 g, 96%) the ¹H-NMR of it showed it to be pure

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enough to use it in the next step.

Examples 23 and 24.

N3-[3-(4-Cyano-4-phenylpiperidino)propyl]-2-oxo-4,4-diphenyl-oxazolidine-3-carboxamide hydrochloride and N3-[3-(4,4-Diphenylpiperidino)propyl]-2-oxo-4,4-diphenyl-oxazolidine-3-carboxamide hydrochloride

a) 1,1-Diphenyl-2-hydroxyethylamine.

To stirred a solution of 2,2-diphenylglycine (5.0 g, 22 mmol) in THF (100 mL) at 0°C under argon atmosphere, a solution of LAH in THF (1M, 50 mL, 50 mmol) was added over a period of 15 minutes and the mixture was allowed to warm to room temperature. After 12 h, it was poured onto a mixture of ice (300 g) and 6N HCl (20 mL) and stirred for 1h. The mixture was basified to pH 10-11 by the addition of 6N NaOH and extracted with dichloromethane (4 X 100 mL). The combined extracts were dried (sodium sulfate) and the solvent evaporated to leave the product as a pale yellow viscous oil, which on trituration with hexane became white powder (4.7 g, ~100%). The ¹H-NMR showed this product to be pure and was used as is in the next step.

b) 4,4-Diphenyl-2-oxo-oxazolidine.

A mixture of 1,1-diphenyl-2-hydroxyethylamine (4.26 g, 20 mmol), CDI (3.24 g, 20 mmol) in dichloromethane (200 mL) was refluxed for 20 h and the solvent evaporated. The residue was purified by column chromatography on silica gel using dichloromethane/ethyl acetate (9:1) to give the product as a viscous oil which solidified on standing (4.25 g, 89%).

c) 4,4-Diphenyl-1-(4-nitrophenyloxycarbonyl)-2-oxo-oxazolidine.

To a stirred suspension of sodium hydride (60% suspension in paraffin, 0.6 g, 15 mmol, 1.5 eq.) in THF (20 mL) at 0 °C, a solution of 4,4-diphenyl-2-oxo-

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oxazolidine (2.39 g, 10 mmol) in THF (5 mL) was added and stirred for 30 minutes. This suspension was added to a solution of 4-nitrophenyl chloroformate (2.41 g, 12 mmol) in THF (20 mL) at -78 °C under argon and the stirring was continued for 2 h. It was slowly warmed to room temperature and after 4 h the solvent was evaporated. The residue was mixed with dichloromethane (150 mL), washed with 0.05 N sodium hydroxide (3 X 10 mL), and dried (sodium sulfate). Solvent was evaporated and the residue was purified by column chromatography on silica gel using chloroform/ethyl acetate (9:1) as the eluent to give the product as a white powder (3.72 g, 92%).

d) General procedure: Examples 23 and 24.

A mixture of 4,4-diphenyl-3-(4-nitrophenyloxycarbonyl)-2-oxo-oxazolidine (40 mg, 0.1 mmol) and an appropriate amine (0.15 mmol, 1.5 eq.) in THF (5 mL) was stirred at room temperature and the product formed was purified by preparative TLC on silica gel using ethyl acetate as the eluent. The HCl salt was made by treatment with 1N HCl in ether.

N3-[3-(4-Cyano-4-phenylpiperidino)propyl]-2-oxo-4,4-diphenyl-oxazolidine-3-carboxamide hydrochloride

Yield 93%; m.p.139-141 °C; Anal. Calcd. For:

$C_{31}H_{32}N_4O_3 \cdot HCl \cdot 0.8CH_2Cl_2$: C, 60.77; H, 5.92; N, 9.51.
Found: C, 60.90; H, 5.80; N, 9.66.

N3-[3-(4,4-Diphenylpiperidino)propyl]-2-oxo-4,4-diphenyl-oxazolidine-3-carboxamide hydrochloride

Yield 92%; m.p.145-148 °C; Anal. Calcd. For:

$C_{34}H_{37}N_3O_3 \cdot HCl \cdot 1.3CH_2Cl_2$: C, 62.12; H, 6.00; N, 6.16.
Found: C, 62.19; H, 5.64; N, 6.14.

Examples 25, 26, 27, 28 and 29.

a. 1-(3,4-Difluorophenyl)-2-methyl-2-hydroxypropylamine.

To a well-stirred solution of methyl 2-amino-2-(3,4-

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5 difluorophenyl)acetate (10.5 g, 52.19 mmol) in anhydrous ether (200 mL) at 0°C a solution of methylmagnesium bromide (3M, 87 mL, 261 mmol) in ether was added in 10 minutes. The mixture was stirred at 0°C for 2.5 h and
10 allowed to warm to room temperature. After 12 h, the mixture was carefully poured onto a mixture of ice (300 g) and saturated ammonium chloride (50 g). The ether layer was separated and the aqueous layer was extracted with more ether (4 X 200 mL). The combined extracts
15 were dried with magnesium sulfate and the solvent evaporated. The crude product was purified by column chromatography on silica gel using chloroform/methanol/2M ammonia in methanol (1000:20:10 mL, 1000:40:20 mL, 1000:80:40 mL) as eluents to give the
20 product as an oil (6.5 g, 62%). The ¹H-NMR and MS confirmed this to be the desired product.

b. 4-(3,4-Difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine.

20 A mixture of 1-(3,4-difluorophenyl)-2-methyl-2-hydroxypropylamine (3.00 g, 14.9 mmol), CDI (2.418 g, 14.9 mmol) in dichloromethane (150 mL) was refluxed for 36 h and the solvent evaporated. The residue was purified by column chromatography on silica gel using chloroform/ethyl acetate (9:1) to give the product as a
25 viscous oil which solidified on standing (1.80 g, 50%).

c. 4-(3,4-Difluorophenyl)-5,5-dimethyl-2-oxo-3-(4-nitrophenyloxycarbonyl)oxazolidine.

30 To a stirred suspension of sodium hydride (60% suspension in paraffin 203 mg, 1.4 eq.) in THF (20 mL) at 0 °C, a solution of 4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine (870 mg, 3.622 mmol) in THF (5 mL) was added and stirred for 30 minutes. This suspension was added to a solution of 4-nitrophenyl
35 chloroformate (950 mg, 4.71 mmol) in THF (20 mL) at -78

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°C under argon and the stirring was continued for 2 h. It was slowly warmed to room temperature and after 4 h the solvent was evaporated. The residue was mixed with dichloromethane (150 mL), washed with 0.05 N sodium hydroxide (3 X 10 mL), and dried (sodium sulfate). Solvent was evaporated and the residue was purified by column chromatography on silica gel using chloroform/ethyl acetate (9:1) as the eluent to give the product as a white powder (860 mg, 59%).

d. General procedure:

A mixture of 4-(3,4-difluorophenyl)-5,5-dimethyl-3-(4-nitrophenyloxycarbonyl)-2-oxo-oxazolidine (50 mg, 0.123 mmol) and an appropriate amine (0.16 mmol, 1.3 eq.) in dichloromethane (6 mL) was stirred at room temperature and the product formed was purified by preparative TLC on silica gel using two elutions, first with chloroform/ethyl acetate (9:1) and then with chloroform/methanol (9:1) as eluents. The HCl salt was made by treatment with 1N HCl in ether.

Example 25:

Methyl 1-[3-([4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine-3-yl]carbonylamino)propyl]-4-phenyl-4-piperidinecarboxylate hydrochloride

Yield 56%; m.p. 208-210 °C; Anal. Calcd. For:

$C_{28}H_{33}F_2N_3O_5 \cdot HCl$: C, 59.41; H, 6.05; N, 7.42. Found: C, 59.06; H, 5.83; N, 7.27.

Example 26:

1-[3-([4-(3,4-Difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine-3-yl]carbonylamino)propyl]-4-phenyl-4-piperidyl acetate hydrochloride

Yield 29%; m.p. 116-118 °C; Anal. Calcd. For:

$C_{28}H_{33}F_2N_3O_5 \cdot HCl \cdot 0.3CH_2Cl_2$: C, 57.46; H, 5.90; N, 7.50. Found: C, 57.38; H, 6.18; N, 7.67.

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Example 27:

N3-3-[4-(2-Pyridyl)piperidino]-3-methylpropyl-4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine-3-carboxamide dihydrochloride

5 Yield 64%; m.p. 87-90 °C; Anal. Calcd. For:
 $C_{26}H_{32}F_2N_4O_3 \cdot 2HCl \cdot 1.1CHCl_3 \cdot 1.1H_2O$: C, 45.81; H, 5.29; N, 7.88. Found: C, 45.73; H, 5.50; N, 8.07.

Example 28:

10 **N3-[3-(4-Cyano-4-phenylpiperidino)-2-hydroxypropyl]-4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine-3-carboxamide hydrochloride**

Yield 63%; m.p. 135-137 °C; Anal. Calcd. For:
 $C_{27}H_{30}F_2N_4O_4 \cdot HCl \cdot 1.2H_2O$: C, 56.83; H, 5.90; N, 9.82.
15 Found: C, 56.88; H, 5.98; N, 9.58.

Example 29:

N3-[3-(4-Cyano-4-phenylpiperidino)-2-fluoropropyl]-4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine-3-
20 **carboxamide hydrochloride**

Yield 39%; m.p. 120-122 °C; Anal. Calcd. For:
 $C_{27}H_{29}F_3N_4O_3 \cdot HCl \cdot 0.8CH_2Cl_2$: C, 53.95; H, 5.15; N, 9.05.
Found: C, 53.89; H, 5.33; N, 8.95.

Example 30:

Methyl 1-5-[4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidin-3-yl]pentyl-4-phenyl-4-piperidinecarboxylate
hydrochloride

a. **4-(3,4-Difluorophenyl)-5,5-dimethyl-1-(5-**
30 **bromopentyl)-2-oxo-oxazolidine.**

To a stirred suspension of sodium hydride (60%
suspension in paraffin 205 mg, 1.4 eq) in THF (20 mL) at
0 °C, a solution of 4-(3,4-difluorophenyl)-5,5-dimethyl-
2-oxo-oxazolidine (880 mg, 3.622 mmol) in THF (5 mL) was
35 added and stirred for 30 minutes. To this 1,5-

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dibromopentane (3.37 g, 14.64 mmol, 4 eq.) and HMPA (179 mg, 3.66 mmol) were added and the mixture was warmed to room temperature. It was heated at 55-60 °C for 12 h and the solvent evaporated. The residue was purified by column chromatography on silica gel using chloroform/ethyl acetate (9:1) as the eluent to give the product as a viscous oil (1.1 g).

b. Methyl 1-5-[4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidin-3-yl]pentyl-4-phenyl-4-

piperidinecarboxylate hydrochloride

A mixture of 4-(3,4-difluorophenyl)-5,5-dimethyl-1-(5-bromopentyl)oxazolidinone (50 mg, 0.123 mmol), 4-phenyl-4-methoxycarbonylpiperidine (0.16 mmol, 1.3 eq.), potassium iodide (11.6 mg), and potassium carbonate (58 mg, 0.42 mmol, 3 eq.) in acetone (6 mL) was stirred and refluxed for 12 h and the product formed was purified by preparative TLC on silica gel using ethyl acetate as the eluent. The HCl salts were made by treatment with 1N HCl in ether. Yield 50%; m.p. 58-60 °C; Anal. Calcd. For: $C_{29}H_{36}F_2N_2O_4 \cdot HCl \cdot 0.8CH_2Cl_2$: C, 57.82; H, 6.28; N, 4.53. Found: C, 58.01; H, 6.53; N, 4.45.

Example 31:

N3-2-[4-(2-Oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidino]ethyl-4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine-3-carboxamide hydrochloride

a. N-(2-[[4-(2-Keto-1-benzimidazoliny]piperidin-1-yl]-ethyl)phthalimide.

To a solution of 4-(2-keto-1-benzimidazoliny]piperidine (5 g, 23 mmol) and N-(2-bromoethyl)phthalimide (5.85 g, 23 mmol) in DMF (100 mL) was added potassium carbonate (10 g) and potassium iodide (250 mg) and the mixture was stirred and heated at 65-70 °C for 2h. It was poured

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into ice-water (500 mL), extracted with ether (4 X 75 mL) and dried (sodium sulfate). Solvent was evaporated and the product was crystallized from methanol (8 g, 89%).

5 **b. N-(2-[[4-(2-Keto-1-benzimidazoliny]piperidin-1-yl]-ethyl)amine**

A mixture of N-(2-[[4-(2-keto-1-benzimidazoliny]piperidin-1-yl]-ethyl)phthalimide (3.9 g, 10 mmol) and hydrazine (2 mL) in methanol was
10 refluxed for 10 h and the solvent was evaporated. The residue was suspended in chloroform (50 mL) and filtered. The residue was washed with more chloroform (50 mL). Solvent was evaporated from the combined filtrate and the residue was dried under vacuum to leave
15 the desired product, which was used in the next step without further characterization.

c. N3-2-[4-(2-Oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidino]ethyl-4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine-3-carboxamide hydrochloride

20 Prepared from 4-(3,4-difluorophenyl)-5,5-dimethyl-3-(4-nitrophenyloxycarbonyl)-2-oxo-oxazolidine (20 mg) and N-(2-[[4-(2-keto-1-benzimidazoliny]piperidin-1-yl]-ethyl)amine (20 mg) as described earlier. Yield 25 mg;
[α]_D = +58.8 (c = 0.40 g, methanol); m.p. 227-230 °C;
25 Anal. Calcd. For: C₂₆H₂₉F₂N₅O₃.HCl.0.4 CH₂Cl₂: C, 54.30; H, 5.32; N, 11.99. Found: C, 54.52; H, 5.40; N, 11.82.

Example 32:

30 **4-(3,4-Difluorophenyl)-3-[(3-[4-(2-pyridyl)piperidino]methylpiperidino)carbonyl]-oxazolidine-2-one dihydrochloride.**

a. 1-Benzyl-4-[pyrid-2-yl]pyridinium bromide.

A solution of 2,4'-dipyridyl (15.62 g, 0.1 mol) and benzyl bromide (17.104 g, 0.1mol) in anhydrous EtOAc

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(600 mL) for 24 h. The pale yellow crystalline product formed was filtered and dried (32.7 g, 100%).

b. 1-Benzyl-4-(2-pyridyl)-1,2,3,6-tetrahydropyridine.

To a stirred solution of 1-benzyl-4-[pyrid-2-yl]pyridinium bromide (50 g, 0.152 mol) in ethanol (500 mL) at 0-5 °C, was added NaBH₄ (23 g) in small portions over a period of 4 h. The mixture was allowed to warm to room temperature and the stirring continued for overnight. Solvent was evaporated the residue was mixed with ether (500 mL), washed with 6N sodium hydroxide solution (200 mL), brine (500 mL), and dried (potassium carbonate). Solvent was evaporated and the oily residue was used in the next step immediately without purification (33.4 g, 88%).

c. 4-(2-Pyridyl)piperidine.

To a solution of 1-benzyl-4-(2-pyridyl)-1,2,3,6-tetrahydropyridine (25 g, 0.1 mol) in MeOH (400 mL) and 2M ammonia in methanol (100 mL), was added Pearlman's catalyst (6 g). The suspension was hydrogenated under 200 psi for 24 h after which the reaction mixture was filtered through a pad of celite and the solvent was removed. The residue was purified by column chromatography over silica gel using CH₂Cl₂/methanol/2M NH₃ in MeOH (45:4:2 to 9:4:4) as the eluting system. The product was obtained as a pale yellow oil (12.4 g, 79%).

d. N-(t-Butyl-carbonate)-nipecotic acid. To a solution of nipecotic acid (3.865 g, 29.9 mmol) in dioxane (20 mL) at 0°C was added (Boc)₂O (6.53 g, 29.9 mmol) and a solution of NaOH (2.63 g, 6.60 mmol) in water (10 mL). The resulting mixture was stirred overnight while warmed up to room temperature. The mixture was concentrated and the residue was acidified to pH=3 with 1 N HCl and then extracted with EtOAc (3 X 50 mL), dried (MgSO₄) to

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afford crude product which was used in the next step without further purification.

e. 4-(2-Pyridyl)piperidine-N-(t-butyl-carbonate)-nipecotamide. To a solution of N-(t-butyl-carbonate)-nipecotic acid (6.85 g, 29.8 mmol) in CH_2Cl_2 (40 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DMAPECD) (11.426 g, 59.6 mmol) and DMAP (9.102 g, 74.5 mmol), then 4-(2-pyridyl)piperidine (4.834 g, 29.8 mmol) was added. The resulting mixture was stirred for 24 hours and quenched with water (40 mL). The mixture was extracted with CH_2Cl_2 (3 X 40 mL) and the combined extracts were dried (K_2CO_3) and concentrated. The residue was purified by flash chromatography on silica gel (CHCl_3 -MeOH- NH_3 , 100:4:1) to afford the product as an oil (5.469 g, 49%).

f. 4-(2-Pyridyl)-N-(2-piperidinyl)methyl-piperidine. A solution of 4-(2-pyridyl)piperidine-N-(t-butyl-carbonate)-nipecotamide (1.904 g, 5.084 mmol) in TFA (5.0 mL) was stirred at 0 °C overnight. The mixture was concentrated and the residue was dissolved in THF (30 mL). The mixture was cooled to 0 °C and lithium aluminium hydride (LAH) (193 mg, 5.084 mmol) was added slowly. The reaction mixture was stirred for 12 hours while warmed to r.t. before quenched with water (1.0 mL) and 1 N NaOH (0.5 mL). The mixture was basified to pH=10 with 1 N NaOH and extracted with CH_2Cl_2 (5 X 20 mL), dried (K_2CO_3) and concentrated. The residue was purified by flash chromatography (CHCl_3 -MeOH- NH_3 , 100:10:2 to 100:20:5) to afford the product as an oil (0.804 g, 61%).

g. 4-(3,4-Difluorophenyl)-3-[(3-[4-(2-pyridyl)piperidino]methylpiperidino)carbonyl]-oxazolidine-2-one dihydrochloride.

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Prepared from 4-(3,4-difluorophenyl)-3-(4-nitrophenyloxycarbonyl)-2-oxo-oxazolidine and 4-(2-pyridyl)-N-(2-piperidinyl)methyl-piperidine following the procedure described earlier.

- 5 Yield 90%; m.p.= 176-178 °C; Anal. Calcd. For $C_{26}H_{31}N_4O_3F_2 \cdot 2HCl \cdot 1.2H_2O \cdot 1.2CH_2Cl_2$: C, 47.90; H, 5.59, N, 8.21. Found: C, 47.27; H, 5.41; N, 8.21.

Example 33:

- 10 **N1-[2-(4-Cyano-4-phenylpiperidino)ethyl]-2-[4-(3,4-difluorophenyl)-2-oxo-oxazolidin-3-yl]acetamide hydrochloride**

- a. (+)-(2-[(4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-1-acetic acid benzyl ester. To a stirred a solution of 4-(3,4-difluorophenyl)-2-oxo-oxazolidinone (398 mg, 2 mmol) in THF (20 mL) at 0 °C under argon atmosphere, LiHMDS (1M solution in THF, 2.2 mL, 2.2 mmol) was added and the mixture was warmed to room temperature. After 30 minutes it was cooled to 0 °C and to this benzyl bromoacetate (0.504 g, 2.2 mmol, 1.1 eq.) was added and the mixture was warmed to room temperature. After 12 h, solvent was evaporated and the residue was purified by column chromatography on silica gel using chloroform/ethyl acetate (9:1) as the eluent to give the product as a viscous oil (0.695 g, 88%).

- 25 b. (+)-(2-[(4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-1-acetic acid

- The product obtained from the above reaction (0.592 g, 1.5 mmol) was dissolved in methanol/water (25/5 mL), mixed with Pearlman's catalyst (120 mg) and hydrogenated at 100 psi for 3 h. The catalyst was removed by filtration and washed with methanol (20 mL). Solvent was evaporated from the combined filtrate to obtain the product as a white powder (0.375 g, 97%).

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c. N1-[2-(4-Cyano-4-phenylpiperidino)ethyl]-2-[4-(3,4-difluorophenyl)-2-oxo-oxazolidin-3-yl]acetamide hydrochloride

A mixture of

- 5 (+)-(2-[(4-(3,4-difluorophenyl)-2-oxo-oxazolidine-1-acetic acid (51.4 mg, 0.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg), and 4-(N,N-dimethylamino)pyridine (100 mg), 2-[(4-cyano-4-phenyl)piperidin-1-yl]propylamine (55 mg) in
10 anhydrous dichloromethane (15 mL) was stirred at room temperature for 12 h. The mixture was diluted with 10 mL of dichloromethane and washed with saturated aqueous ammonium chloride solution (6 X 10 mL). Solvent was
15 evaporated from the dried (sodium sulfate) dichloromethane solution and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent, to obtain the desired product as a white powder (82 mg);
20 $[\alpha]_D = +168.40$ (c = 0.42 g, methanol). The HCl salt was prepared by treatment of a solution of the free base in ether with 1N HCl in ether. M.p. 136-139 °C; Anal. Calcd. for $C_{25}H_{27}N_4O_3F_2Cl \cdot 0.4CH_2Cl_2$: C, 56.38; H, 5.20; N, 10.40. Found: C, 56.38; H, 5.30; N, 10.52.

25 **Example 34:**

4-{4-[4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carbonyl]-piperazin-1-yl}-1-phenyl-cyclohexanecarbonitrile

a. 1-Phenyl-4-piperazin-1-yl-cyclohexanecarbonitrile

- 30 A mixture of 4-cyano-4-phenyl-cyclohexanone (0.23 g, 1.2 mmol) and piperazine (0.30 g, 3.5 mmol) in 20 ml of toluene was stirred at reflux for 2 h in presence of catalytic amount of p-toluenesulfonic acid. The reaction mixture was concentrated in vacuo to provide a
35 white solid, which was redissolved in 20 ml of EtOH and

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stirred with NaBH₄ (0.30 g, 80 mmol) for 12 h at 25 °C. Reaction mixture was diluted with 100 ml of EtOAc and washed with brine several times. Organic layer was dried over MgSO₄ and concentrated in vacuo, to provide oily residue, which was subjected to column chromatography (10% MeOH/EtOAc) to yield 0.13 g (40%) of the desired product as an oil.

b. 4-{4-[4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carbonyl]-piperazin-1-yl}-1-phenyl-cyclohexanecarbonitrile

To a solution of 4-(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid 4-nitrophenyl ester (80 mg, 0.21 mmol) in 5 ml of THF was added 1-phenyl-4-piperazin-1-yl-cyclohexanecarbonitrile (80 mg, 0.29 mmol) in a portion and the resulting solution was stirred for 12 h at 25 °C. Reaction mixture was concentrated in vacuo yielding a yellow oil, which was subjected to column chromatography (50% Hexane/EtOAc) to provide 53 mg (51%) of the desired product as a colorless oil. The product obtained was converted to the HCl salt and recrystallized from EtOAc-Et₂O to afford 43 mg of the product as white solid: mp 148-151 °C; Anal. Calc. For C₂₇H₂₈F₂N₄O₃·1.0HCl requires C, 61.07; H, 5.50; N, 10.55. Found: C, 59.48; H, 5.41; N, 10.34.

Example 35:

(+)-4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(4-furan-2-yl-4-phenyl-piperidin-1-yl)-propyl]-amide

a. 4-Phenyl-4-furan-2-yl-piperidine

To a solution of 4-hydroxy-4-phenyl-piperidine (0.50 g, 2.8 mmol) in 10 ml of CH₂Cl₂ at 25 °C was added furan (0.40 ml, 5.6 mmol) and aluminum chloride (0.75 g, 5.6 mmol) in a portion and the resulting heterogeneous

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solution was stirred for 3 h. Reaction mixture was poured into cold aqueous NaHCO_3 and extracted with EtOAc. Organic layer was dried over Na_2SO_4 and concentrated in vacuo to provide oily residue, which was purified by column chromatography (30% NH_3 sat'd MeOH/EtOAc) to yield 0.48 g (76%) of the desired product as an oil.

b. 3-[4-(4-furan-2-yl-4-Phenyl-phenyl)-piperidin-1-yl]]-propyl-1-amine

A solution of the amine (0.15 g, 0.66 mmol), (3-bromopropyl)-carbamic acid tert-butyl ester (0.30 g, 1.3 mmol) and K_2CO_3 (1.0 g, 7.4 mmol) in 10 ml of dioxane was stirred at reflux for 12 h. Reaction mixture was diluted with EtOAc and washed with brine several times. Organic layer was dried over Na_2SO_4 and concentrated in vacuo to provide oily residue, which was purified by column chromatography (EtOAc, neat) to yield 120 mg of the desired product as tert-butyl carbamic ester. The ester was diluted in 5 ml of CH_2Cl_2 and 1 ml of trifluoroacetic acid, and stirred for 2 h at 25 °C. Reaction mixture was concentrated in vacuo, yielding an oil, which was diluted with EtOAc and washed with aqueous NaHCO_3 . Organic layer was dried over Na_2SO_4 and concentrated in vacuo to provide 86 mg (33%) of the desired product as a colorless oil.

c. (+)-4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid [3-(4-furan-2-yl-4-phenyl-piperidin-1-yl)-propyl]amide

To a solution of (+)-4-(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid 4-nitrophenyl ester (19 mg, 0.05 mmol) in 5 ml of CH_2Cl_2 was added 3-[4-(4-Phenyl-4-furan-2-yl-phenyl)-piperidin-1-yl]]-propyl-1-amine (12 mg, 0.04 mmol) in a portion and the resulting solution was stirred for 4 h at 25 °C. Reaction mixture was concentrated in vacuo yielding a yellow oil, which

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was subjected to column chromatography (5% MeOH/CHCl₃) to provide 18 mg (88%) of the desired product as a colorless oil. The product obtained was converted to the HCl salt and recrystallized from EtOAc-Et₂O to afford 19 mg of the product as white solid: mp 149-151 °C; [α]_D = + 49.4 (c=0.11, MeOH); Anal. Calc. For C₂₈H₂₉F₂N₃O₄·1.0HCl requires C, 62.42; H, 5.42; N, 7.53. Found: C, 60.79; H, 5.49; N, 7.43.

Example 36:

(+)-4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(1-methyl-1H-pyrrol-2-yl)-4-phenyl-piperidin-1-yl]-propyl}-amide

a. 4-Phenyl-4-(1-methyl-pyrrol)-2-yl-piperidine

To a solution of 4-hydroxy-4-phenyl-piperidine (0.50 g, 2.8 mmol) in 10 ml of CH₂Cl₂ was added 1-methyl-pyrrole (0.51 ml, 5.6 mmol) and aluminum chloride (0.75 g, 5.6 mmol) in a portion and the resulting heterogeneous solution was stirred for 4 h at -78 °C. Reaction mixture was poured into cold aqueous NaHCO₃ and extracted with EtOAc. Organic layer was dried over Na₂SO₄ and concentrated in vacuo to provide oily residue (0.81 g), which was identified as the desired product by NMR analysis and subjected to the following reaction without any further purification.

b. 3-[4-(1-methyl-1H-pyrrol-2-yl)-4-phenyl-piperidin-1-yl]-propyl-1-amine

A solution of the amine (0.81 g, 2.8 mmol), (3-bromo-propyl)-carbamic acid tert-butyl ester (1.0 g, 4.2 mmol), K₂CO₃ (1.0 g, 7.4 mmol) and NaI (0.05 g) in 10 ml of dioxane was stirred at reflux for 12 h. Reaction mixture was diluted with EtOAc and washed with brine several times. Organic layer was dried over Na₂SO₄ and concentrated in vacuo to provide oily residue, which was purified by column chromatography (2% MeOH/CHCl₃) to

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yield 0.87 g (78%) of the desired product as tert-butyl carbamic ester. The ester was diluted in 10 ml of CH_2Cl_2 and 1 ml of trifluoro-acetic acid, and stirred for 2 h at 25 °C. Reaction mixture was concentrated in vacuo, yielding an oil, which was diluted with EtOAc and washed with aqueous NaHCO_3 . Organic layer was dried over Na_2SO_4 and concentrated in vacuo to provide 0.63 g (75% for two steps) of the desired product as a colorless oil.

c. (+)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(1-methyl-1H-pyrrol-2-yl)-4-phenyl-piperidin-1-yl]-propyl}-amide

To a solution of (+)-4-(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid 4-nitrophenyl ester (30 mg, 0.08 mmol) in 5 ml of CH_2Cl_2 was added 3-[[4-phenyl-4-(1-methyl-pyrrol)-2-yl-phenyl]-piperidin-1-yl]-propyl-1-amine (24 mg, 0.08 mmol) in a portion and the resulting solution was stirred for 4 h at 25 °C. Reaction mixture was concentrated in vacuo yielding a yellow oil, which was subjected to column chromatography (5% MeOH/ CHCl_3) to provide 14.4 mg (34%) of the desired product as a colorless oil. The product obtained was converted to the HCl salt and recrystallized from EtOAc-Et₂O to afford 13.0 mg of the product as white solid: mp 135-138 °C; $[\alpha]_D = +34.1$ (c=0.11, MeOH); Anal. Calc. For $\text{C}_{28}\text{H}_{29}\text{F}_2\text{N}_3\text{O}_4 \cdot 1.0\text{HCl}$ requires C, 62.42; H, 5.42; N, 7.53. Found: C, 60.79; H, 5.49; N, 7.43.

Example 37:

(+)-4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(5-methyl-thiophen-2-yl)-piperidin-1-yl]-propyl}-amide

a. 4-[4-Hydroxy-4-(5-methyl-thiophen-2-yl)]-piperidine

To a solution of 2-methyl-thiophene (1.0 ml, 10 mmol) in 40 ml of dry THF was added tert-butyl lithium (1.7 M

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solution in ether, 6.5 ml, 11 mmol) dropwise and the resulting solution was stirred for 1 h at -40 °C. To the solution was added N-tert-butoxycarbonyl-4-piperidinone (1.0 g, 5.0 mmol) in a portion and the resulting solution was stirred for 2 h. Reaction was quenched by adding a few drops of water. Reaction mixture was diluted with EtOAc and washed with brine several times. Organic layer was dried over Na₂SO₄ and concentrated in vacuo to provide an oil, which was identified as the desired product by NMR analysis and subjected to the following reaction without any further purification.

b. 4-(5-Methyl-thiophen-2-yl)-piperidine

A solution of the carbamic ester (1.3 g, 4.4 mmol) and triisopropylsilane (1.0 ml, 8.2 mmol) in 10 ml of CH₂Cl₂ was added 10 ml of trifluoroacetic acid and the resulting solution was stirred for 2 h at 0 °C. Reaction mixture was concentrated in vacuo, yielding a dark oil, which was redissolved in EtOAc and washed with aqueous NaHCO₃. Organic layer was dried over Na₂SO₄ and concentrated in vacuo to provide oily residue, which was purified by column chromatography (5% MeOH/CHCl₃) to yield 0.73 g (87%) of the desired product as an oil.

c. 3-[4-(5-methyl-thiophene-2-yl)-piperidin-1-yl]-propyl-1-amine

A solution of the amine (0.73 g, 4.0 mmol), (3-bromopropyl)-carbamic acid tert-butyl ester (1.8 g, 7.5 mmol), K₂CO₃ (1.0 g, 7.4 mmol) and NaI (0.05 g) in 25 ml of acetone was stirred at reflux for 12 h. Reaction mixture was diluted with EtOAc and washed with brine several times. Organic layer was dried over Na₂SO₄ and concentrated in vacuo to provide oily residue, which was purified by column chromatography (5% MeOH/CHCl₃) to yield 0.60 g (44%) of the desired product as tert-butyl carbamic ester. The ester was diluted in 10 ml of

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CH₂Cl₂ and 1 ml of trifluoroacetic acid, and stirred for 2 h at 25 °C. Reaction mixture was concentrated in vacuo, yielding an oil, which was diluted with EtOAc and washed with aqueous NaHCO₃. Organic layer was dried over Na₂SO₄ and concentrated in vacuo to provide 0.40 g of the desired product as a colorless oil.

d. (+)-4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid (3-[4-(5-methyl-thiophen-2-yl)-piperidin-1-yl]-propyl)-amide

To a solution of (+)-4-(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid 4-nitrophenyl ester (46 mg, 0.12 mmol) in 5 ml of CH₂Cl₂ was added 3-[4-(5-methyl-thiophen-2-yl)-piperidin-1-yl]-propyl-1-amine (30 mg, 0.13 mmol) in a portion and the resulting solution was stirred for 12 h at 25 °C. Reaction mixture was concentrated in vacuo yielding a yellow oil, which was subjected to column chromatography (5% MeOH/CH₂Cl₂) to provide 41 mg (74%) of the desired product as a colorless oil. The product obtained was converted to the HCl salt and recrystallized from EtOAc-Et₂O to afford 43 mg of the product as white solid: mp 143-146 °C; [α]_D = + 41.0 (c=0.11, MeOH); Anal. Calc. For C₂₃H₂₇F₂N₃O₄·1.0HCl requires C, 55.25; H, 5.64; N, 8.40. Found: C, 57.01; H, 5.54; N, 8.29.

General Procedure for the Preparation of the 4,4-Diaryl

Piperidines: A mixture of 0.5 g of 4-aryl-4-hydroxy piperidine, 3 mL of the aromatic substrate, and 1 g of aluminum chloride were stirred at room temperature for 3 days. The reaction mixture was poured over 10 mL of ice, diluted with t-butyl-methyl ether, the resulting hydrochloride salt was filtered, washed with water and ether, dried, and used in the next step after spectral

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characterization.

4-Phenyl-4-(4-thiomethoxy-phenyl)-piperidine,

5 **Hydrochloride:** From 4-phenyl-4-hydroxy-piperidine and thioanisole (82%), Anal. Calc. for $C_{18}H_{21}N_1S_1+HCl+0.2H_2O$: C, 66.83; H, 6.98; N, 4.33. Found: C, 66.71; H, 6.81; N, 4.24.

4-(4-Fluoro-phenyl-4-(4-thiomethoxy-phenyl)-piperidine,

10 **Hydrochloride:** From 4-(4-fluoro-phenyl-4-hydroxy-piperidine and thioanisole (59%), Anal. Calc. for $C_{18}H_{20}F_1N_1S_1+HCl+0.35CH_2Cl_2$: C, 60.14; H, 5.56; N, 3.90. Found: C, 59.96; H, 5.95; N, 3.81.

4-(4-Fluoro-phenyl-4-(2-methoxy-5-fluoro-phenyl)-

15 **piperidine, Hydrochloride:** From 4-(4-fluoro-phenyl)-4-hydroxy-piperidine and 4-fluoroanisole (78%), Anal. Calc. for $C_{18}H_{19}N_1F_2O_1+HCl+0.2H_2O$: C, 62.96; H, 5.99; N, 4.08. Found: C, 62.72; H, 6.06; N, 4.06.

20 **Bis-(4-fluoro-phenyl)piperidine, Hydrochloride:** From 4-(4-fluoro-phenyl)-4-hydroxy-piperidine and 3 mL of fluorobenzene (69%).

4-(4-Bromo-phenyl-4-(4-methoxy-phenyl)-piperidine,

25 **Hydrochloride:** From 4-(4-bromo-phenyl-4-hydroxy-piperidine and thioanisole (66%), Anal. Calc. for $C_{18}H_{20}Br_1N_1S_1+HCl$: C, 54.21; H, 5.30; N, 3.51. Found: C, 54.43; H, 5.22; N, 3.41.

30 **General Procedure for the Preparation of the 4,4-Diaryl-1-(3-amino-propyl)Piperidines:** A solution of 1.00 mmol of diarylpiperidine, 1.30 mmol of N-BOC-3-bromopropylamine, 1.00 mL of diisopropylethylamine and 2

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mL of dioxane were heated at reflux temperature for 36 hours, cooled, applied to prep-tlc plates and eluted with the appropriate solvent. The product was used in the next step after spectral characterization. A
5 solution of the N-BOC protected amine in 1:1 TFA-water was stirred at room temperature for 2 hours (monitored by tlc), solvent removed in vacuo, the product was dissolved in dichloromethane, washed with saturated Na_2CO_3 solution, dried (Na_2SO_4), solvent removed in
10 vacuo, and the product was used after spectral characterization.

[4-(4-methanesulfonyl-phenyl)-4-phenyl]-3-aminopropyl-piperidine: A mixture of 644 mg of [4-(4-thiomethyl-phenyl)-4-phenyl]-3-aminopropyl-piperidine
15 (TFA salt, 1.13 mmol), 853 mg of 50-60% 3-chlorophenylperbenzoic acid (2.72 mmol, assuming 55% purity), 2 mL of trifluoroacetic acid and 10 mL of chloroform were stirred at room temperature for 36
20 hours, solvent removed in vacuo, and the product was chromatographed (X2) (NH_3 -MeOH- CHCl_3) to give 270 mg of the desired product.

General procedure for the synthesis of Examples 38, 39, 40, 41 and 42.
25

A solution of (+)-4^a(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid 4-nitro-phenyl ester (25 mg, 0.069 mmol), the 4,4-diaryl-1-(3-amino-propyl) piperidine (1.2 equiv.) in 5 ml of methylene chloride
30 were stirred at room temperature for 12 hours. The reaction mixture was washed with 3 N KOH solution. The organic phase was chromatographed on preparative TLC (CH_2Cl_2 /methanol/ 2 N NH_3 in methanol = 40 /2/1) to obtain the title compound. The hydrochloride salt of

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the free base was prepared by addition of 1 N HCl in ether to a solution of the free base in ethyl acetate until no more precipitate was observed.

5 **Example 38:**

4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(4-bromo-phenyl)-4-(4-methoxy-phenyl)-piperidin-1-yl]-propyl}-amide

33 mg of the free base was obtained (55% yield). Anal.
10 Calc. For $C_{31}H_{32}BrF_2N_3O_4 + 1.5 \text{ HCl}$: C, 54.50 %; H, 4.94 %; N, 6.15 %. Found: C, 54.62 %; H, 4.88 %; N, 5.88 %. M.p. of the salt: 123 ~ 126 °C. $[\alpha]_D^{22} = + 53.93$.

15 **Example 39:**

4-(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(4-fluoro-phenyl)-4-(4-methylsulfanyl-phenyl)-piperidin-1-yl]-propyl}-amide

20 mg of the free base was obtained (55% yield). Anal.
20 Calc. For $C_{31}H_{32}F_3N_3O_3S + 1.75 \text{ HCl} + 0.75 \text{ EtOAc}$: C, 57.23 %; H, 5.61 %; N, 5.89 %. Found: C, 57.28 %; H, 5.73 %; N, 5.83 %. M.p. of the salt: 121 ~ 124 °C $[\alpha]_D^{22} = + 33.33$.

25 **Example 40:**

4-(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4,4-bis-(4-fluoro-phenyl)-piperidin-1-yl]-propyl}-amide. 24 mg of the free base was obtained (63 % yield). Anal. Calc. For $C_{30}H_{21}F_4N_3O_3 + 2.0 \text{ HCl} + 0.125 \text{ CHCl}_3$: C, 56.24 %; H, 4.88 %; N, 6.52 %. Found: C, 56.39 %; H, 4.88 %; N, 6.10 %. M.p. of the salt: 124 ~ 126 °C. $[\alpha]_D^{22} = + 47.33$.

30

Example 41:

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4-(3,4-difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(4-fluoro-phenyl)-4-(2-methoxy-5-fluoro-phenyl)-piperidin-1-yl]-propyl}-amide

24 mg of the free base of the tittle product was
5 obtained (59% yield). Anal. Calc. For $C_{31}H_{31}F_4N_3O_4$ + 2.0 HCl + 0.5 EtOAc: C, 56.42 %; H, 5.31 %; N, 5.98 %. Found: C, 56.61 %; H, 5.18 %; N, 5.77 %. M.p. of the salt: 130 ~ 133 °C $[\alpha]_D^{22} = + 38.86$.

10 Example 42:

(+)-4-(3,4-Difluoro-phenyl)-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(4-methanesulfonyl-phenyl)-4-phenyl-piperidin-1-yl]-propyl}-amide, hydrochloride

15 18 mg of the free base was obtained: Anal. Calc. For $C_{31}H_{31}F_4N_3O_4$ + 2.0 HCl + EtOAc: C, 55.41 %; H, 5.71 %; N, 5.54 %. Found: C, 55.82 %; H, 5.19 %; N, 5.49 %.

Example 43:

20 4-(3,4-Difluorophenyl)-1-(3-(4-(2-pyridyl)piperidin-1-yl)-propyl)aminocarbonyl-2-imidazolidone.

a. 2-Amino-2-(3,4-difluorophenyl)-acetonitrile:

To a mixture of 3,4-difluorobenzaldehyde (2.0 g, 14.07 mmol) and trimethylsilylcyanoide (2.34 ml, 17.59 mmol),
25 catalytic amount of Zinc Iodide was added at 0°C. After stirring for 15 minutes at room temperature a saturated solution of methanolic ammonia (15 ml) was added in one lot at 0°C. The reaction mixture was then stirred for 4 hours at 40 °C. After evaporation of the solvent the
30 residue was purified by column chromatography (hexanes:ethyl acetate;3:2) to yield 1.98 g of the product as a brown syrup.

b. 1-(3,4-Difluorophenyl)ethane-1,2-diamine:

To Lithium aluminium hydride in ether (50.7 ml, 50.76

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mmol), at 0°C, cyano amine in ether (80 ml) slowly over a period of 10 minutes. The solution was then allowed to stir at room temperature for 1 hour. The reaction mixture was cooled to 0°C and quenched with water (2 ml), 15% NaOH (2 ml) and water (10 ml). The mixture was then filtered, the residue was repeatedly washed with ethylacetate. The solution was then concentrated to yield 2.71 g (93%) of the crude product as an oil which was then used for the subsequent step.

c. 4-(3,4-Difluorophenyl)-2-imidazolidone:

To the diamine (1.667 g, 9.68 mmol) in dichloromethane (20ml), triethylamine (1.34 ml, 9.68 mmol) was added slowly and the reaction was cooled to -78°C. Then triphosgene (3.01 g, 10.16 mmol) was added to the solution over a period of 30 minutes. The reaction mixture was then stirred at -78°C for 5 minutes. The reaction mixture was quenched with water and partitioned between dichloromethane (20 ml) and water, washed with 10 ml 10% KOH solution, dried over sodium sulfate, filtered and concentrated. The product was then purified by column purified (hexanes:ethyl acetate 2:3) to yield 0.995 g (52%) of a yellow solid.

d. 4-(3,4-Difluorophenyl)-2-imidazolidone-1-carboxylic acid 4-nitrophenyl ester:

To sodium hydride (0.069 g, 2.74 mmol) in THF (10 ml), 4-(3,4-difluorophenyl)-2-imidazolidone (0.5g, 2.49 mmol) was added at 0°C. The solution was then stirred at room temperature for 15 minutes. It was then added to a solution of 4-nitrophenyl chloroformate (0.552g, 2.74 mmol) at -78°C via a cannula. The reaction mixture was then allowed to stir at room temperature for 8 hours. It was then concentrated and partitioned between ethyl acetate (20 ml) and water (5 ml), washed with 10 %KOH (10 ml), dried over sodium sulfate, filtered and concentrated. Purification by column chromatography

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(hexanes:ethylacetate 2:3) yielded 0.04 g (4.4 %) of the product as a light brown syrup.

e. 4-(3,4-Difluorophenyl)-1-(3-(4-(2-pyridyl)piperidin-1-yl)-propyl)aminocarbonyl-2-imidazolidone:

5 To 4-(3,4-difluorophenyl)-1-(4-nitrophenoxy)carbonyl-2-imidazolidone (0.05 g, 0.137 mmol) in THF (10 mL) was added 1-(3-aminopropyl)-4-(2-pyridyl)piperidine (0.036 g, 0.165 mmol) and the solution was stirred at room temperature for 16 hours. The solution was then
10 concentrated and the residue flash chromatographed (ethyl acetate:methanol 4:1) to yield 0.038 g (59%) of the product as a brown syrup. It was dissolved in dichloromethane (2 mL) and treated with 1N HCl in ether (0.5 mL). The solution was concentrated under reduced
15 pressure. Recrystallization of the residue from ether gave 0.029 g (60 %) of the hydrochloride salt as a brown solid: mp 148-150°C. Anal. Calcd. for $C_{23}H_{29}F_2N_4O_3Cl_2 \cdot 0.5 CCl_4$: C, 51.90; H, 4.90; N, 11.0. Found: C, 54.23; H 5.17; N, 10.84.

20

Example 44:

3-(4-(4-Cyano-4-phenylpiperidin-1-yl)piperidin-1-yl)carbonyl-4-(3,4-difluorophenyl)-2-imidazolidone.

a. 4-(3,4-Difluorophenyl)-2-imidazolidone-3-carboxylic acid 4-nitrophenyl ester:

25 To sodium hydride (0.069 g, 2.74 mmol) in THF (10 ml), 4-(3,4-difluorophenyl)-imidazolidin-2-one (0.5g, 2.49 mmol) was added at 0°C. The solution was then stirred at room temperature for 15 minutes. It was then added
30 to a solution of 4-nitrophenylchloroformate (0.552g, 2.74 mmol) at -78°C via a cannula. The reaction mixture was then allowed to stir at room temperature for 8 hours. It was then concentrated and partitioned between ethyl acetate (20 ml) and water (5 ml), washed with 10

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%KOH (10 ml), dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:ethylacetate; 2:3) to yield 0.04 g (4.4 %) of the product as a light brown syrup.

5 **b. 3-(4-(4-Cyano-4-phenylpiperidin-1-yl)piperidin-1-yl)carbonyl-4-(3,4-difluorophenyl)-2-imidazolidone:**

To 4-(3,4-difluorophenyl)-3-(4-nitrophenoxy)carbonyl-2-imidazolidone (0.04 g, 0.110 mmol) in THF (10 mL) was added 4-(4-cyano-4-phenylpiperidin-1-yl)piperidine
10 (0.0355 g, 0.132 mmol) and the solution was stirred at room temperature for 16 hours. The solution was then concentrated and the residue flash chromatographed (ethyl acetate:methanol 4:1) to yield 0.024 g (44%) of the product as a brown syrup. It was dissolved in
15 dichloromethane (2 mL) and treated with 1N HCl in ether (0.5 mL). The solution was concentrated under reduced pressure. Recrystallization of the residue from ether gave 0.029 g (96%) of the hydrochloride salt as a white solid: mp 243-245°C. Anal. Calcd. for $C_{27}H_{30}ClF_2N_5O_2 \cdot 0.4$
20 $CHCl_3$: C, 56.96; H, 5.30; N, 12.12. Found: C, 57.08; H 5.20; N, 11.90.

Example 45

4-(3,4-Difluorophenyl)-3-methyl-1-(3-(4-(2-
25 pyridyl)piperidin-1-yl)propyl)aminocarbonyl-2-imidazolidone.

a. 2-(3,4-Difluorophenyl)-2-methylamino-acetonitrile:

To a mixture of 3,4-difluorobenzaldehyde (4.0 g, 28.0
30 mmol) and trimethylsilylcyanoide (4.69 mL, 35.1 mmol), catalytic amount of Zinc Iodide was added at 0°C. After stirring for 15 minutes at room temperature a saturated solution of methylammonia (15 mL) was added in one lot at 0°C. The reaction mixture was then stirred for 4
35 hours at 40°C. After evaporation of the solvent the

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residue was purified by column chromatography (hexanes:ethylacetate 3:2) to yield 4.719 g (92%) of the product as a brown syrup.

b. 2-(3,4-Difluorophenyl)-2-methylamino-ethylamine:

5 To Lithium aluminum hydride in ether (49.41 mL, 49.4 mmol), at 0°C, 2-(3,4-difluorophenyl)-2-methylamino-acetonitrile (3.0 g, 16.47 mmol) in ether (80 mL) slowly over a period of 10 minutes. The solution was then allowed to stir at room temperature for 1 hour. The
10 reaction mixture was cooled to 0°C and quenched with water (2 mL), 15% NaOH (2 mL) and water (10 mL). The mixture was then filtered, the residue was repeatedly washed with ethylacetate. The solution was then concentrated to yield 2.71 g (93%) of the crude product
15 as an oil.

c. 4-(3,4-Difluorophenyl)-3-methyl-2-imidazolidone:

To 2-(3,4-difluorophenyl)-2-methylamino-ethylamine (1.048 g, 5.68 mmol) in dichloromethane (20mL), 1,1-carbonyldiimidazole (1.09 g, 6.75 mmol) was added slowly
20 and the reaction was stirred at room temperature for 24 hours. It was then concentrated and purified by column chromatography (hexanes:ethylacetate; 1:4) to yield 0.876 g (73%) of a yellow solid.

d. 4-(3,4-Difluorophenyl)-3-methyl-1-(3-(4-(2-pyridyl)piperidin-1-yl)propyl)aminocarbonyl-2-imidazolidone.

To a solution of 4-(3,4-difluorophenyl)-3-methyl-2-imidazolidone (0.15 g, 0.706 mmol) in THF (10 mL) cooled at 0°C, lithium bis(trimethylsilyl)amide in THF (0.848
30 mL, 0.848 mmol) was added slowly and the solution was stirred at room temperature for 15 minutes. After cooling to -78°C, phosgene (0.729 g, 7.06 mmol) was added and the solution was stirred at -78°C for 1 hour. It was then concentrated to give an intermediate
35 (0.194g, 0.703 mmol) which was immediately dissolved in

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THF (10 mL) at -78°C and treated with 1-(3-aminopropyl)-4-(2-pyridyl)piperidine (0.231 g, 1.05 mmol) and triethylamine (0.106 g, 1.055 mmol), and the solution was stirred at room temperature for 24 hours. It was then concentrated, and the residue partitioned between dichloromethane (25 mL) and water (5 mL). The organic layer was washed with 10% KOH solution (5 mL), dried over sodium sulfate, filtered and concentrated. Purification of the residue by flash chromatography (ethyl acetate: methanol 24:1) yielded 0.030 g (9%) of the product as a syrup. It was dissolved in dichloromethane (2 mL) and treated with 1N HCl in ether (0.5 mL). The solution was concentrated under reduced pressure. Recrystallization of the residue from ether gave 0.030 g (88%) of the dihydrochloride salt as a pale yellow solid: mp 120-122°C. Anal. Calcd. for $C_{24}H_{31}ClF_2N_5O_2 \cdot 0.95 CHCl_3$: C, 46.54; H, 5.00; N, 10.88. Found: C, 46.30; H 5.35; N, 11.20.

Example 46:

4-(3,4-Difluorophenyl)-3-(3-(4-(2-methoxyl-5-methyl)phenyl-4-phenyl)piperidin-1-yl)propyl)aminocarbonyl-2-imidazolidone.

a. 1-(3,4-Difluorophenyl)-2-tritylamino-ethylamine:

To a solution of 1-(3,4-difluorophenyl)-ethane-1,2-diamine (6 g, 35.6 mmol) in dichloromethane (100 ml), diazabicycloundecane (DBU) (5.87 mL, 39.2 mmol) was added and the solution cooled to 0°C. Trityl chloride (10.94 g, 39.2 mmol) in dichloromethane (100 ml) was added slowly to the cooled solution. After addition the solution was stirred at room temperature for 24 hours. The solution was then concentrated, partitioned between chloroform (100 ml) and water (25 ml), washed with 1N KOH (10 mL), filtered, and concentrated. Purification by column chromatography (hexanes:ethyl acetate 3:2)

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yielded 6.75 g (46 %) of the product as a brown syrup.

b. 4-(3,4-Difluorophenyl)-1-trityl-2-imidazolidone:

To a solution of 1-(3,4-difluorophenyl)-2-tritylamino-ethylamine (6.75g, 16.44 mmol) in THF (200 mL), 1,1-carbonyldiimidazole (3.2 g, 19.7 mmol) was added and the solution was stirred at room temperature for 12 hours. The solution was concentrated and purified by column chromatography (hexanes:ethylacetate 3:2) to yield 5.55 g (77%) of the product as a white solid.

c. 4-(3,4-Difluorophenyl)-1-trityl-2-imidazolidone-3-carboxylic acid 4-nitrophenyl ester:

To sodium hydride (95 %) (0.189 g, 7.49 mmol) in THF (150 ml), 4-(3,4-Difluorophenyl)-1-trityl-2-imidazolidone (3.0 g, 6.81 mmol) was added at 0°C. The solution was then stirred at room temperature for 15 minutes. It was then added to a solution of 4-nitrophenylchloroformate (1.647 g, 8.17 mmol) at -78°C via a cannula. The reaction mixture was then allowed to stir at room temperature for 12 hours. It was then concentrated and partitioned between ethyl acetate (30 ml) and water (5 ml), washed with 10 %KOH (10 ml), dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexanes:ethylacetate; 2:3) to yield 2.1 g (51%) of the product as a light brown syrup.

d. 4-(3,4-Difluorophenyl)-3-(3-(4-(2-methoxy-5-methyl)phenyl-4-phenylpiperidin-1-

yl)propyl)aminocarbonyl-1-trityl-2-imidazolidone:

To 4-(3,4-difluorophenyl)-3-(4-nitrophenoxy)carbonyl-1-trityl-2-imidazolidone (0.089, 0.147 mmol) in THF (5 mL) was added 3-(4-(2-methoxy-5-methyl)phenyl-4-phenylpiperidin-1-yl)propylamine (0.055 g, 0.162 mmol) and the solution was stirred at room temperature for 16 hours. The solution was then concentrated and the residue flash chromatographed (hexanes:ethyl acetate

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1:4) to yield 0.08 g (68%) of the product as a syrup.

e. 4-(3,4-Difluorophenyl)-3-(3-(4-(2-methoxyl-5-methyl)phenyl)-4-phenylpiperidin-1-yl)propyl)aminocarbonyl-2-imidazolidone:

- 5 To 4-(3,4-Difluorophenyl)-3-(3-(4-(2-methoxyl-5-methyl)phenyl)-4-phenylpiperidin-1-yl)propyl)aminocarbonyl-1-trityl-2-imidazolidone (0.100 g, 0.124 mmol) in dichloromethane (2 mL) at 0°C, trifluoroacetic acid (4 mL) in dichloromethane (2 mL)
- 10 was slowly added and the solution was stirred at room temperature for 20 minutes. The solution was then concentrated, neutralized with 10% KOH and extracted into dichloromethane (20 mL). The organic layer was dried over sodium sulfate, filtered and concentrated.
- 15 Purification of the residue by flash chromatography (ethyl acetate) yielded 0.06 g (87%) of a white foam. To it in dichloromethane (2 mL), 1N HCl in ether (0.5 mL) was added, and the solution concentrated under reduced pressure. Recrystallization of the residue from ether
- 20 gave 0.061 g (96 %) of a hydrochloride salt as a white solid: mp 173-175°C. Anal. Calcd. for $C_{32}H_{36}ClF_2N_4O_3 \cdot 1.20 CHCl_3$: C, 53.72; H, 5.19; N, 7.55. Found: C, 53.76; H 5.01; N, 7.36.

25 **Example 47:**

(-)-3-(3-(4-Cyano-4-phenylpiperidin-1-yl)-2(S)-methylpropyl)-aminocarbonyl-4-(3,4-difluorophenyl)-2-imidazolidone.

30 **a. 4-Cyano-1-(3-hydroxy-2(S)-methylpropyl)-4-phenylpiperidine:**

- A mixture of 4-cyano-4-phenylpiperidine hydrochloride (1.89 g, 8.49 mmol) and (S)-3-bromo-2-methyl-1-propanol (1.0 g, 6.53 mmol), potassium carbonate (2.709 g, 19.6 mmol) and sodium iodide (1.17 g, 7.84 mmol) in acetone
- 35 (20 mL) was refluxed for 12 hours. The solution was

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cooled to room temperature and concentrated. The residue was partitioned between ethyl acetate (25 mL) and water (10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Purification of the residue by flash chromatography (hexanes:ethyl acetate 2:3) yielded 1.45 g (86%) of the product as a syrup.

b. 1-(3-Azido-2(S)-methylpropyl)-4-cyano-4-phenylpiperidine:

To a solution of 4-cyano-1-(3-hydroxy-2(S)-methylpropyl)-4-phenylpiperidine (1.0 g, 3.87 mmol), triphenyl phosphine (1.01 g, 3.87 mmol) and diethyl azodicarboxylate (0.609 g, 3.87 mmol) in THF (20 mL) was slowly added diphenylphosphorylazide (0.83 mL, 3.87 mmol) and the solution was stirred at room temperature for 24 hours. The solution was then concentrated and flash chromatographed (hexanes:ethyl acetate 3:2) to yield 0.963 g (88%) of the product as a light brown syrup.

c. 1-(3-Amino-2(S)-methylpropyl)-4-cyano-4-phenylpiperidine:

To a solution of 1-(3-azido-2(S)-methylpropyl)-4-cyano-4-phenylpiperidine (0.96 g, 3.39 mmol) in ethyl acetate (10 mL) was added trimethylphosphine (8.4 mL, 8.49 mmol) and water (0.30 mL, 16.9 mmol) and the solution was stirred at room temperature for 24 hours. The solution was then concentrated and flash chromatographed (ethyl acetate:methanol:methanolic ammonia 3:1:1) to yield 0.60 g (69%) of the crude product as a syrup.

d. (-)-3-(3-(4-Cyano-4-phenylpiperidine-1-yl)-2(S)-methylpropyl)-aminocarbonyl-4-(3,4-difluoro)phenyl-1-trityl-2-imidazolidone:

To 4-(3,4-difluoro)phenyl-3-(4-nitrophenoxy)carbonyl-1-trityl-2-imidazolidone (0.49 g, 0.809 mmol) in THF (10 mL) was added 1-(3-amino-2(S)-methylpropyl)-4-cyano-4-

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phenylpiperidine (0.250 g, 0.92 mmol) and the solution was stirred at room temperature for 16 hours. The solution was then concentrated and flash chromatographed (ethyl acetate:methanol 4:1) to yield 0.441 g (73%) of the product as a syrup.

e. (-)-3-(3-(4-Cyano-4-phenylpiperidin-1-yl)-2(S)-methyl)propyl-aminocarbonyl-4-(3,4-difluorophenyl)-2-imidazolidone:

To (-)-3-(3-(4-Cyano-4-phenylpiperidine-1-yl)-2(S)-methylpropyl)-aminocarbonyl-4-(3,4-difluoro)phenyl-1-trityl-2-imidazolidone (0.441 g, 0.607 mmol) in dichloromethane (2 mL) at 0°C was added trifluoroacetic acid (4 mL) in dichloromethane (2 mL) and the solution was stirred at room temperature for 20 minutes. The solution was then concentrated, neutralized with 10% KOH and extracted into dichloromethane (20 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Purification of the residue by column chromatography (ethyl acetate) yielded 0.293 g (100%) of the product as a syrup. The two diastereomers were separated by using Chiralcel OD (20 x 250 mm) column with hexanes/2-propanol/diethylamine (60:40:0.1) as the eluent.

To the desired diastereomer (0.016 g, 0.0332 mmol) in dichloromethane (2 mL) was added 1N HCl in ether (0.5 mL) and the solution concentrated under reduced pressure. Recrystallization of the residue from ether gave 0.016 g (94%) of the hydrochloride salt as a white solid: $[\alpha]_D = -5.32$ (8.0 mg/mL MeOH); mp 265-267°C. Anal. Calcd. for $C_{26}H_{30}ClF_2N_5O_2 \cdot 0.15 CHCl_3$: C, 58.61; H, 5.67; N, 12.07. Found: C, 58.50; H 5.90; N, 12.10.

Example 48:

(+)-3-(3-(4-cyano-4-(2,4-dichloro)phenylpiperidin-1-yl)propyl)aminocarbonyl-4-(3,4-difluorophenyl)-2-

oxazolidinone.

a. 4-Cyano-4-(2,4-dichlorophenyl)-piperidine-1-carboxylic acid tert-butyl ester:

To bis(2-chloroethyl)-carbamic acid tert-butyl ester
5 (1.0g, 3.8 mmol) and (2,4-dichloro)phenyl
acetonitrile(0.708 g, 3.8 mmol) in DMF (35 mL) was added
NaH (95 %) (0.258 g, 9.68 mmol) in one lot at 0°C. The
solution was stirred for 10 minutes at room temperature.
When the foaming subsided, the solution was heated at
10 60°C for 24 hours. It was then quenched with water at
0°C and concentrated. The residue was extracted with
ethyl acetate (25 mL) and washed with water (3 x 15 mL).
The organic layer was dried over sodium sulfate,
filtered and concentrated. Purification of the residue
15 by column chromatography (hexane:ethyl acetate 4:1)
yielded 0.620 g (45%) of the product as a syrup.

b. {3-[4-Cyano-4(2,4-dichlorophenyl)-piperidin-1-yl]-propyl}-carbamic acid tert-butyl ester:

To 4-cyano-4-(2,4-dichlorophenyl)-piperidine-1-
20 carboxylic acid tert-butyl ester (0.620 g, 1.74 mmol) in
dichloromethane (5 mL), trifluoroacetic acid (2 mL) was
added and the solution stirred at room temperature for 1
hour. The solution was concentrated, neutralized with
10 % KOH solution and extracted into 25 ml of
25 dichloromethane. The organic layer was dried over
sodium sulfate, filtered and concentrated to give 0.442
g (99%) of 4-(2,4-dichlorophenyl)-piperidine-4-
carbonitrile which was used as such for the subsequent
step.

30 To a stirred solution of the 4-(2,4-
dichlorophenyl)piperidine-4-carbonitrile (0.736 g, 2.88
mmol) in acetone (20 mL) was added N-(tert-
butoxycarbonyl)-3-bromopropylamine (0.754 g, 3.17 mmol,
potassium carbonate (1.594 g, 11.53 mmol) and sodium

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iodide (0.865 g, 5.7 mmol) and the solution refluxed for 24 hours. The reaction mixture was cooled to room temperature, concentrated and partitioned between chloroform (30 mL) and water (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate) to yield 0.925 g (78 %) of the required product as a colorless oil.

c. (+)-3-(3-(4-cyano-4-(2,4-dichloro)phenyl)piperidin-1-yl)propyl)aminocarbonyl-4-(3,4-difluorophenyl)-2-oxazolidinone:

To 3-[4-cyano-4-(2,4-dichlorophenyl)-piperidin-1-yl]-propyl-carbamic acid tert-butyl ester (0.589, 1.42 mmol) in dichloromethane (5 mL), trifluoroacetic acid (1 mL) was added and the solution stirred at room temperature for 1 hour. The solution was concentrated, neutralized with 10 % KOH solution and extracted into 25 mL of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated to give 0.423 g (93%) of 1-(3-aminopropyl)-4-(2,4-dichlorophenyl)-piperidine-4-carbonitrile which was used as such for the subsequent step.

To 4-(3,4-difluorophenyl)-2-oxazolidinone-3-carboxylic acid 4-nitrophenyl ester (0.03 g, 0.0823 mmol) in dry THF (10 mL) was added 1-(3-aminopropyl)-4-(2,4-dichlorophenyl)piperidine-4-carbonitrile (0.03 g, 0.0823 mmol) and the solution was stirred at room temperature for 24 hours. The reaction mixture was concentrated and purified by column chromatography (hexanes:ethyl acetate 1:4) to yield 0.04 g (91%) of the product as a foamy syrup. To the syrup (0.040 g, 0.0744 mmol) in 4 mL of dichloromethane, 5 mL of 1N HCl in ether was added, and the solution concentrated under reduced pressure. Recrystallization of the residue from

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ether gave 0.040 g (94 %) of the product as a white solid: mp 204-206 °C; $[\alpha]_D = 48.8$ (1.55 mg/mL MeOH).
Anal. Calcd. for $C_{25}H_{25}F_2N_4O_3Cl_2 \cdot 0.60 CH_2Cl_2$: C, 49.21; H, 4.21; N, 8.97. Found: C, 49.44; H 4.39; N, 8.66.

5

Example 49:

(+)-3-(3-(4-Aminocarbonyl-4-(4-chloro)phenyl)piperidin-1-yl)-propylaminocarbonyl-4-(3,4-difluoro)phenyl-2-oxazolidinone.

10 **a. 3-(4-Cyano-4(4-chlorophenyl)piperidin-1-yl)propylcarbamic acid tert-butyl ester:**

To bis(2-chloroethyl)-carbamic acid tert-butyl ester (1.0 g, 3.8 mmol) and (4-chloro)phenyl acetonitrile (0.624 g, 4.12 mmol) in DMF (35 mL) was added NaH (95
15 %) (0.260 g, 10.30 mmol) in one lot at 0°C. The solution was stirred for 10 minutes at room temperature. When the foaming subsided, the solution was heated at 60°C for 45 minutes. It was then quenched with water at 0°C, partitioned between ethyl acetate (25 mL) and
20 brine (3 x 20 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to yield 0.76 g (56 %) of the crude product which was used as such for the subsequent step.

25 To 4-cyano-4-(4-chlorophenyl)piperidine-1-carboxylic acid tert-butyl ester (0.85 g, 2.64 mmol) in dichloromethane (2 mL) was added 2 mL of trifluoroacetic acid and the solution stirred at room temperature for 1 hour. The solution was concentrated, neutralized with
30 10 % KOH solution and extracted into 25 mL of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (ethyl acetate:methanol:methanolic
35 ammonia 8:1:1) yielded 0.482 g (82 %) of the product as

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a syrup.

b. 3-(4-(4-Chlorophenyl)-4-cyanopiperidin-1-yl)propylcarbamic acid tert-butyl ester:

To a stirred solution of the 4-(4-chlorophenyl)piperidine-4-carbonitrile (0.482 g, 2.18 mmol) in acetone (20 mL) was added N-(tert-butoxycarbonyl)-3-bromopropylamine (0.572 g, 2.4 mmol, potassium carbonate (1.20 g, 8.7 mmol) and sodium iodide (0.655 g, 4.36 mmol) and the solution refluxed for 24 hours. The reaction mixture was cooled to room temperature, concentrated and partitioned between chloroform (20 mL) and water (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate) to yield 0.655 g (71 %) of the required product as a colorless oil.

c. (+)-3-(3-(4-Aminocarbonyl-4-(4-chloro)phenyl)piperidin-1-yl)-propylaminocarbonyl-4-(3,4-difluoro)phenyl-2-oxazolidinone:
3-(4-(4-chlorophenyl)-4-cyanopiperidin-1-yl)propylcarbamic acid tert-butyl ester (0.150 g, 5.39 mmol) in conc. H_2SO_4 (1 mL) was stirred at room temperature for 30 hours. The solution was concentrated, neutralized with 10 % KOH solution and extracted into 25 mL of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated to give 0.185 g (79%) of 1-(3-aminopropyl)-4-(4-chlorophenyl)piperidine-4-carboxamide which was used as such for the subsequent step.

To 4-(3,4-difluorophenyl)-3-(4-nitrophenoxy)carbonyl-2-oxazolidinone (0.040 g, 0.109 mmol) in 10 mL of dry THF was added 1-(3-aminopropyl)-4-(4-chlorophenyl)-piperidine-4-carboxamide (0.042 g, 0.141 mmol) and the solution was stirred at room temperature for 24 hours. The reaction mixture was

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concentrated and purified by column chromatography (ethyl acetate: MeOH 9:1) to yield 0.025 g (44%) of the product as a foamy syrup. To the syrup (0.025 g, 0.048 mmol) in dichloromethane (2 mL) was added 1N HCl in ether (0.5 mL) and the solution concentrated under reduced pressure. Recrystallization of the residue from ether gave 0.021 g (80 %) of the product as a white solid: mp 140-142 °C; $[\alpha]_D = 52.0$ (1.3 mg/mL MeOH). Anal. Calcd. for $C_{25}H_{27}Cl_2F_2N_4O_4 \cdot 1.7 CH_2Cl_2$: C, 45.70; H, 4.51; N, 7.96. Found: C, 45.75; H 4.64; N, 7.96.

Example 50:

(+)-3-(5-(4-Cyano-4-phenylpiperidin-1-yl)pent-2(E)-en-1-yl)-4-(3,4-difluoro)phenyl-2-oxazolidinone.

To a solution of 4-(3,4-difluorophenyl)-2-oxazolidinone (0.2 g, 1 mmol) and HMPA (0.18 g, 1 mmol) in THF (6 mL) was added NaH (44 mg, 1.1 mmol, 60% in mineral oil) at room temperature. After 30 min, 1,5-dibromo-2-pentene (0.34 g, 1.5 mmol) was added to the mixture. the mixture was stirred at room temperature for 4 h. After removal of solvent, the residue was flash chromatographed over silica gel (1:1 hexane-ethyl acetate) to give a mixture of two isomers in 40% yield as a yellow oil.

This oil (0.14 g, 0.4 mmol) was mixed with 4-cyano-4-phenylpiperidine hydrochloride (0.18 g, 0.8 mmol), potassium carbonate (0.2 g, 1.4 mmol), sodium iodide (61 mg, 0.4 mmol) in acetone (6 mL) and was refluxed overnight. After removal of the solvent, the residue was flash chromatographed over silica gel (ethyl acetate) to give a mixture of two isomers in 22% yield as a yellow oil. HPLC separation (column: Primesphere SiO_2 5 μ m, 21.2 x 250 mm, eluent: 75:25:0.1 ethyl acetate-hexane-triethylamine) gave the desired product (20 mg) as a yellow oil. It was treated with 1.0 equivalent of HCl to give a salt as a yellow solid: mp 168-170°C; ESMS m/e =

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452 (MH⁺); $[\alpha]_D = 45.0$ (0.4 mg/mL CH₂Cl₂). Anal. Calcd. for C₂₆H₂₇F₂N₃O₂·HCl·1.0H₂O: C, 61.72; H, 5.98; N, 8.30. Found: C, 61.79; H, 5.88; N, 8.26.

5 **Example 51: trans (+)-4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid{3-[4-(4-fluoro-2-methylphenyl)-piperidin-1-yl]propyl}amide**

10 a. 3-[4-(4-fluoro-2-methylphenyl)-piperidin-1-yl]-propylamine was synthesized as described in Example 22, Step c, and was used in the next step without further purification.

15 **b. trans (+)-4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid{3-[4-(4-fluoro-2-methylphenyl)-piperidin-1-yl]propyl}amide**

20 As described in Example 18, step i, the trans (+)-4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.03 g, 0.08 mmol) was converted into trans (+)-4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid{3-[4-(4-fluoro-2-methylphenyl)-piperidin-1-yl]propyl}amide, using the side chain described in step a above, with 75% yield. It was converted into the hydrochloride salt. M.P. = 80-83°C; $[\alpha]_D = + 23.0$ (c = 0.12, MeOH); Anal. Calcd. for C₂₅H₂₉N₃O₃F₃Cl·0.23 H₂O: C, 58.91; H, 5.98; N, 7.93. Found: C, 58.91; H, 6.37; N, 7.73.

25 **Example 52: (+)-8-(3,4-Difluorophenyl)-6-oxo-5-oxa-7-aza-spiro[3.4]octan-7-carboxylic acid-{3-[4-(4-fluoro)phenyl)-piperidin-1-yl]-propyl}-amide**

30 **a. Benzhydrylindene-(3,4-difluoro-benzyl)-amine**

To a solution of 3,4-difluorobenzylamine (9.8 g, 69 mmol) and benzophenone (13.0 g, 71.0 mmol) in toluene (200 mL) was added a catalytic amount of BF₃·OEt₂ and the resulting solution was stirred at reflux for 12 h.

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The reaction mixture was concentrated in vacuo, yielding an oil (21 g, >95%), which was characterized by NMR analysis and subjected to the following reaction without any further purification.

5 **b. 1-[(Benzhydryliden-amino)-(3,4-difluoro-phenyl)methyl]-cyclobutanol**

To a solution of the imine (2.5 g, 8.1 mmol) in 50 mL of dry THF was added tert-butyllithium (1.7 M, 6.2 mL) dropwise and the resulting solution was stirred at -78°C
10 for 0.5 h. To the solution was added cyclobutanone (0.74 ml, 9.9 mmol) in 10 ml of THF and the solution was stirred at -78 °C for 2 h and 25 °C for 1 h. The reaction was quenched by adding 1.0 mL of dilute acetic acid. Reaction mixture was diluted with 100 ml of Et₂O
15 and washed with brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo, yielding 1-[(benzhydryliden-amino)-(3,4-difluoro-phenyl)methyl]-cyclobutanol as an oil, which was subjected to the following reaction without purification.

20

c. 1-[Amino-(3,4-difluoro-phenyl)methyl]-cyclobutanol

The crude batch of 1-[(benzhydryliden-amino)-(3,4-difluoro-phenyl)methyl]-cyclobutanol obtained from the above reaction and MeONH₂.HCl (1.35 g, 16.2 mmol) was
25 dissolved in 125.0 mL of MeOH and stirred for 12 h. The reaction mixture was concentrated in vacuo, yielding oily residue which was redissolved in 100 ml of EtOAc and was washed with 2.0 M NaOH followed by brine. The organic layer was separated, dried over Na₂SO₄ and then
30 concentrated in vacuo to give 1-[amino-(3,4-Difluoro-phenyl)methyl]-cyclobutanol as an oil which was used in the next step without any purification.

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d. [(3,4-Difluorophenyl)-(1-hydroxy-cyclobutyl)-methyl]-carbamic acid-tert-butyl ester

To a solution of 1-[amino-(3,4-difluoro-phenyl)methyl]-cyclobutanol (approximately 8.1 mmol) in CH₂Cl₂ (50 mL)
5 at 0°C was added a solution of di-tert-butyl dicarbonate (3.5 g, 16.2 mmol) in one portion and the resulting solution was stirred for 2 h at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (9:1
10 cyclohexane-EtOAc followed by 4:1 cyclohexane-EtOAc) to obtain [(3,4-difluorophenyl)-(1-hydroxy-cyclobutyl)-methyl]-carbamic acid-tert-butyl ester as a viscous oil (1.0 g, 40% yield over four steps).

15 e. 8-(3,4-Difluorophenyl)-5-oxa-7-aza-spiro[3.4]octan-6-one

To a well stirred solution of [(3,4-difluorophenyl)-(1-hydroxy-cyclobutyl)-methyl]-carbamic acid-tert-butyl ester (1.0 g, 3.2 mmol) in THF (20 mL) was added 95% NaH
20 (0.2 g, 8.3 mmol) at room temperature. The resulting suspension was stirred for 3 h at about 35°C (warm water bath) and then quenched carefully with ice. The biphasic mixture was extracted with 100 mL of EtOAc, washed with brine, dried over Na₂SO₄, filtered and the
25 solvent was removed in vacuo to yield 8-(3,4-difluorophenyl)-5-oxa-7-aza-spiro[3.4]octan-6-one in racemic form as a white solid.

The (+) and (-) enantiomers were separated by HPLC by using Chiralcel OD (4.6 x 250 mm) using 80%
30 hexane/20% isopropyl alcohol/ 0.1 % diethylamine as the eluting system (12 mL/min) under isothermal conditions (U.V. 254 nm). The retention times for the two isomers

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of were 12.1 min {[a]_D = - 20.0 (c = 0.35, MeOH)} and 15.6 min {[a]_D = + 23.7 (c = 0.52, MeOH)} respectively. The (-)-enantiomer was used in the next step (0.30g, 35% yield).

5

f. (+)-8-(3,4-Difluorophenyl)-6-oxo-5-oxa-7-aza-spiro[3.4]octan-7-carboxylic acid-4-nitrophenyl]ester

To a solution of (-)-8-(3,4-difluorophenyl)-5-oxa-7-aza-spiro[3.4]octan-6-one (0.15 g, 0.63 mmol) in 10 mL THF
10 was added a solution of n-butyllithium in hexane (0.47 mL, 0.76 mmol) dropwise via a syringe under argon atmosphere at -78°C. The resulting yellow solution was stirred at -78°C for 50 min. This solution was then added dropwise via a cannula into another round bottom
15 flask containing a solution of 4-nitrophenylchloroformate (0.15 g, 0.76 mmol) in 10 mL of THF, cooled at -78°C, over a period of 15 min. After five minutes, the flask was removed from the cooling bath and stirring was continued for 1 h. The reaction
20 was quenched by adding ice and it was extracted with EtOAc. The organic extracts were washed with brine and the organic layer was dried over Na₂SO₄. The solvent was removed after filtration and the residue was purified by column chromatography on silica gel with 4:1
25 cyclohexane-ethyl acetate to obtain (+)-8-(3,4-difluorophenyl)-6-oxo-5-oxa-7-aza-spiro[3.4]octan-7-carboxylic acid-4-nitrophenyl]ester as a thick syrup which solidified upon standing (0.19 g, 75%). [a]_D = + 42.0 (c = 0.65, MeOH).

30

g. (+)-8-(3,4-Difluorophenyl)-6-oxo-5-oxa-7-aza-spiro[3.4]octan-7-carboxylic acid-(3-[4-(4-

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fluoro)phenyl)-piperidin-1-yl]-propyl}-amide

To a solution of 3-[4-(4-fluorophenyl)piperidin-1-yl]propylamine (0.02 g, 0.08 mmol) in 10 mL of THF (+)-8-(3,4-difluorophenyl)-6-oxo-5-oxa-7-aza-spiro[3.4]octan-7-carboxylic acid-4-nitrophenyl]ester (0.02 g, 0.05 mmol) was added and the resulting yellow solution was stirred under argon atmosphere for 10 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAc followed by 15% MeOH in EtOAc as the eluting systems (R_f = 0.4, 1:3 MeOH/EtOAc) to obtain (+)-8-(3,4-difluorophenyl)-6-oxo-5-oxa-7-aza-spiro[3.4]octan-7-carboxylic acid-{3-[4-(4-fluoro)phenyl)-piperidin-1-yl]-propyl}-amide as a pale yellow oil (0.02 g, 89%). It was converted into its hydrochloride salt by dissolving it into 5 mL of EtOAc and then treating it with 1.0 mL of HCl in Et₂O (1.0 M). Mass spectrum showed M+1 peak.

Example 53: (+)-5-Cyclopropyl-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-{3-[4-(4-fluoro-2-methyl-phenyl)-piperidin-1-yl]-propyl}-amide

a. 2-(Benzhydryliden-amino)-1-cyclopropyl-2-(3,4-difluoro-phenyl)-ethanol

To a solution of benzhydrylindene-(3,4-difluoro-benzyl)-amine (2.5 g, 8.1 mmol) in 50 mL of dry THF was added tert-butyllithium (1.7 M, 6.2 mL) dropwise and the resulting solution was stirred at -78°C for 0.5 h. To the solution was added cyclopropanecarboxaldehyde (0.90 mL, 12.0 mmol) in 10 mL of THF and the solution was stirred at -78 °C for 2 h and 25 °C for 1 h. The reaction was quenched by adding 1.0 mL of dilute acetic

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acid. Reaction mixture was diluted with 100 ml of Et₂O and washed with brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo, yielding 2-(benzhydryliden-amino)-1-cyclopropyl-2-(3,4-difluorophenyl)-ethanol as a yellow oil, which was subjected to the following reaction without purification.

b. 2-Amino-1-cyclopropyl-2-(3,4-difluorophenyl)-ethanol

The crude batch of 2-(benzhydryliden-amino)-1-cyclopropyl-2-(3,4-difluorophenyl)-ethanol obtained from the above reaction (approximately 16.2 mmol) and MeONH₂.HCl (4.0 g, 48.0 mmol) was dissolved in 125.0 mL of MeOH and stirred for 12 h. The reaction mixture was concentrated in vacuo, yielding oily residue which was redissolved in 100 ml of EtOAc and was washed with 2.0 M NaOH followed by brine. The organic layer was separated, dried over Na₂SO₄ and then concentrated in vacuo to give the crude product as a yellow oil. It was purified by column chromatography over silica gel (95:5 CHCl₃/10% ammonia in MeOH) to yield 3.2 g (93% yield) of 2-amino-1-cyclopropyl-2-(3,4-difluorophenyl)-ethanol as a pale yellow oil.

c. [2-Cyclopropyl-1-(3,4-difluorophenyl)-2-hydroxyethyl]-carbamic acid-tert-butyl ester

To a solution of 2-amino-1-cyclopropyl-2-(3,4-difluorophenyl)-ethanol (1.7 g, 8.1 mmol) in CH₂Cl₂ (50 mL) at 0°C was added a solution of di-tert-butyl dicarbonate (3.5 g, 16.2 mmol) in one portion and the resulting solution was stirred for 2 h at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (4:1 cyclohexane/EtOAc) to obtain [2-cyclopropyl-1-(3,4-

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difluorophenyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester as a viscous oil (1.7 g, 68% yield).

e. 5-Cyclopropyl-4-(3,4-Difluorophenyl)-oxazolidin-2-one

- 5 To a well stirred solution of [2-cyclopropyl-1-(3,4-difluorophenyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester (1.7 g, 5.4 mmol) in THF (20 mL) was added 95% NaH (0.4 g, 16.2 mmol) at room temperature. The resulting suspension was stirred for 3 h at about 35°C
- 10 (warm water bath) and then quenched carefully with ice. The biphasic mixture was extracted with 100 mL of EtOAc, washed with brine, dried over Na₂SO₄, filtered and the solvent was removed in vacuo to yield 5-cyclopropyl-4-(3,4-difluorophenyl)-oxazolidin-2-one (1.3 g, 93% yield)
- 15 as a 3:1 mixture of the trans:cis diastereomers. The diastereomers were separated by column chromatography over silica gel with 7:3 cyclohexane/ethyl acetate as the eluting system. The trans isomer eluted first (R_f = 2.5, 0.65 g) followed by the cis isomer (R_f = 2.0, 0.2 g). The relative stereochemistry was assigned by
- 20 comparing the ¹H NMR of the two isomers of 5-cyclopropyl-4-(3,4-difluorophenyl)-oxazolidin-2-one to the corresponding isomers of 4-(3,4-difluorophenyl)-5-methyl-oxazolidin-2-one as described in Example 19.
- 25 The (+) and (-) enantiomers of the trans-isomer were separated by HPLC by using Chiralcel OD (4.6 x 250 mm) using 80% hexane/20% isopropyl alcohol/ 0.1 % diethylamine as the eluting system (12 mL/min) under isothermal conditions (U.V. 254 nm). The retention
- 30 times for the two enantiomers were 12.0 min {[α]_D = +1.8 (c = 0.35, MeOH)} and 15.5 min respectively. The (+)-enantiomer was used in the next step.

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f. (+)-5-Cyclopropyl-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitrophenyl]ester

To a solution of (+)-5-cyclopropyl-4-(3,4-Difluorophenyl)-oxazolidin-2-one (0.16 g, 0.66 mmol) in 10 mL THF was added a solution of n-butyllithium in hexane (0.49 mL, 0.79 mmol) dropwise via a syringe under argon atmosphere at -78°C. The resulting yellow solution was stirred at -78°C for 50 min. This solution was then added dropwise via a cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (0.16 g, 0.79 mmol) in 10 mL of THF, cooled at -78°C, over a period of 15 min. After five minutes, the flask was removed from the cooling bath and stirring was continued for 1 h. The reaction was quenched by adding ice and it was extracted with EtOAc. The organic extracts were washed with brine and the organic layer was dried over Na₂SO₄. The solvent was removed after filtration and the residue was purified by column chromatography on silica gel with 4:1 cyclohexane-ethyl acetate to obtain (+)-5-cyclopropyl-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitrophenyl]ester as a thick syrup (0.17 mg, 58%).

g. (+)-5-Cyclopropyl-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-(3-[4-(4-fluoro-2-methyl-phenyl)-piperidin-1-yl]-propyl)-amide

To a solution of 3-[4-(4-fluoro-2-methyl-phenyl)-piperidin-1-yl]propylamine (0.02 g, 0.05 mmol) in 10 mL of CH₂Cl₂, (+)-5-cyclopropyl-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitrophenyl]ester (0.01 g, 0.03 mmol) was added and the

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resulting yellow solution was stirred for 10 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAc followed by 15% MeOH in EtOAc as the eluting systems (R_f = 0.4, 1:3 MeOH/EtOAc) to obtain (+)-5-cyclopropyl-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-(3-[4-(4-fluoro-2-methylphenyl)-piperidin-1-yl]-propyl)-amide as a pale yellow oil (0.01 g, 80%). It was converted into its hydrochloride salt by dissolving it into 5 mL of EtOAc and then treating it with 1.0 mL of HCl in Et₂O (1.0 M). Mass spectrum showed M+1 peak.

Example 54: Asymmetric Synthesis of 4-(3,4-Difluorophenyl)-5-methyl-oxazolidin-2-one

a. 2-Hydroxy-1-pyrrolidin-1-yl-propan-1-one (The procedure reported by Vilarrasa et al. Tetrahedron Lett. 1997, 38, 1633 was used; see also Scheme 31)

S-(+)-Methyl lactate (48.03 mmol, 5.0 g) and pyrrolidine (52.8 mmol, 4.4 mL) were mixed in a round bottom flask and the reaction mixture was allowed to stir at room temperature for four days. Methanol was distilled off using a short path distillation apparatus to obtain 2-hydroxy-1-pyrrolidin-1-yl-propan-1-one as a yellow oil. It was used in the next reaction without further purification.

b. 2-(tert-Butyl-dimethyl-silanyloxy)-1-pyrrolidin-1-yl-propan-1-one

To a solution of 2-hydroxy-1-pyrrolidin-1-yl-propan-1-one (47.0 mmol, 6.72 g) in DMF (25 mL) was added imidazole (70.5 mmol, 4.8 g), N,N-dimethyl-4-

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aminopyridine (4.7 mmol, 0.57 g) at room temperature. Tert-butyl-dimethylsilyl chloride (48.5 mmol, 7.31 g) was then added while stirring. Some exotherm was observed. The initial pale yellow solution turned brown in color and some precipitate was observed after 30 min. The reaction mixture was allowed to stir overnight and then filtered through a sintered glass funnel. The solid was washed with some Et₂O. The filtrate was diluted with water (150 mL) and it was extracted with Et₂O (2 X 100 mL). The organic extracts were combined and washed successively with water (100 mL), sat. NH₄Cl solution and the organic layer was separated. It was dried over Na₂SO₄, filtered and the solvent was removed in vacuo to obtain 2-(tert-butyl-dimethyl-silanyloxy)-1-pyrrolidin-1-yl-propan-1-one as a golden yellow oil (10.4 g, 86% yield). The product was judged to be > 95% pure by NMR and was used in next step without any purification.

c. 2-(tert-Butyl-dimethyl-silanyloxy)-1-(3,4-difluorophenyl)-1-yl-propan-1-one

To a round bottom flask containing 72.0 mL of THF at -78°C was added a solution of n-butyllithium in hexane (72.0 mmol, 45.0 mL) under an argon atmosphere followed by 1-bromo-3,4-difluorobenzene (72.0 mmol, 8.1 mL). A solution of 2-(tert-butyl-dimethyl-silanyloxy)-1-pyrrolidin-1-yl-propan-1-one (60.0 mmol, 15.4 g) in 10.0 mL THF was then added in a steady stream and the orange colored solution was stirred for 35 min at -78°C. It was quenched with 20.0 mL of sat. NH₄Cl solution and was allowed to attain room temperature. The solution was extracted with Et₂O (2 X 50 mL), washed with brine and the organic layer was dried over Na₂SO₄. The solution

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was filtered and the solvent was removed in vacuo to obtain the product as an orange oil. The crude product was subjected to silica gel flash column chromatography (9:1 hexane/EtOAc to 4:1 hexane/EtOAc as the eluent system). 2-(tert-Butyl-dimethyl-silanyloxy)-1-(3,4-difluoro-phenyl)-1-yl-propan-1-one was obtained as a pale yellow oil (14.1 g, 78% yield, 96% based on the recovered starting material).

d. 2-(tert-Butyl-dimethyl-silanyloxy)-1-(3,4-difluoro-phenyl)-1-yl-propan-1-one-oxime

To a solution of 2-(tert-Butyl-dimethyl-silanyloxy)-1-(3,4-difluoro-phenyl)-1-yl-propan-1-one (13.7 mmol, 4.1 g) in 60.0 mL of methanol was added sodium acetate (mmol, 3.76 g) and hydroxylamine hydrochloride (mmol, 1.24 g) and the resulting solution was stirred at room temperature overnight. Methanol was then removed in vacuo and the resulting residue was extracted with EtOAc (2 X 50 mL) and brine. The organic layer was separated, dried over Na₂SO₄, filtered and the solvent was removed in vacuo. 2-(tert-Butyl-dimethyl-silanyloxy)-1-(3,4-difluoro-phenyl)-1-yl-propan-1-one-oxime was obtained as a colorless oil (4.04 g, 94% yield). It was used in the next step without further purification.

e. 1-Amino-1-(3,4-difluorophenyl)-propan-2-ol

To a solution of 2-(tert-butyl-dimethyl-silanyloxy)-1-(3,4-difluoro-phenyl)-1-yl-propan-1-one-oxime (12.2 mmol, 3.84 g) in 20.0 mL of Et₂O was added a 1.0 M solution of lithium aluminum hydride (25.0 mmol, 25.0 mL) at 0°C under an argon atmosphere. After 1 h, the solution was heated to reflux for 2 h at which time some solid was observed. The reaction mixture was cooled to

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0°C and then quenched sequentially with water (1.0 mL), 1.0 N KOH (1.0 mL) and water (3.0 mL). The residue was filtered and the solid was washed with warm Et₂O (20.0 mL). The filtrates were combined and dried over Na₂SO₄.

5 The solution was filtered and the solvent was removed in vacuo to obtain 1-amino-1-(3,4-difluorophenyl)-propan-2-ol as a colorless oil as a mixture of two diastereomers which solidified into a low melting solid (2.1 g, 92% yield). It was used in the next step without
10 purification.

It was converted into 4-(3,4-difluorophenyl)-5-methyl-oxazolidin-2-one by the general procedure as described before.

**f. [1-(3,4-Difluorophenyl)-2-hydroxy-propyl]-carbamic
15 acid-tert-butyl ester**

To a solution of 1-amino-1-(3,4-difluorophenyl)-propan-2-ol (3.5 g, 19.1 mmol) in CHCl₃ (15 mL) at 0°C was added a solution of di-tert-butyl dicarbonate (5.1 g, 23.6 mmol) in CHCl₃ (10 mL) in one portion and the
20 resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (2:1 hexane-EtOAc followed by EtOAc) to obtain [1-(3,4-difluorophenyl)-2-hydroxy-propyl]-carbamic acid-
25 tert-butyl ester as a viscous oil (3.3 g, 60.2%).

g. 4-(3,4-Difluorophenyl)-5-methyl-oxazolidin-2-one

To a well stirred solution of [1-(3,4-difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester (0.43 g, 1.5 mmol) THF (20 mL) was added 95% NaH (0.09 g, 3.8
30 mmol) at room temperature. The resulting suspension was stirred for 3 h at about 35°C (warm water bath) and then quenched carefully with ice. The biphasic mixture was

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extracted with 100 mL of EtOAc, washed with brine, dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The two diastereomers were separated by column chromatography over silica gel (First isomer: 0.11 g, R_f = 0.6, 3:1 hexane-EtOAc; second isomer: 0.23 g, R_f = 0.5, 3:1 hexane-EtOAc). NOE experiment suggested that the first diastereomer had the methyl and the aryl group in trans configuration while the second diastereomer had cis relationship between the two groups.

Each diastereomer was subjected to chiral HPLC analysis using Chiralcel OD (4.6 x 250 mm) using 80% hexane/20% isopropyl alcohol/ 0.1% diethylamine as the eluting system (12 mL/min) under isothermal conditions (U.V. 254 nm). The retention time for the trans-oxazolidinone was 13.0 min. This corresponds to the (+)-isomer of the trans oxazolidinone that was synthesized by a separate method as described in Example 19 (the retention time for the (+)-trans-oxazolidinone was 12.1 min). The HPLC analysis also confirmed that the enantiomeric purity of the diastereomer was >99% because no peak corresponding to (-)-isomer was observed. Since the absolute stereochemistry of the starting material [(S)-(+)-methyl lactate] is known, the absolute stereochemistry of the (+)-isomer of the trans-oxazolidinone must be (S,S) at the two stereocenters.

This enantiomerically pure oxazolidinone can be converted into the required final products by using similar methodology as described before in example 19.

General synthetic schemes: In addition to the specific examples of compounds described above, typical procedures for the synthesis of the compounds of this invention are shown in Schemes 32-35. In Scheme 34, the

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synthesis may be carried out using a procedure similar to Koo, J. (J. Am. Chem. Soc., 1953, 75, 723), Anderson, P. (Tetrahedron Lett., 1971, 2787), and Bean, N. P. et al. (Tetrahedron, 1993, 49, 3193). In Scheme 35, the
5 synthesis may be carried out using a procedure similar to Belkon, Y. et al. (J. Chem. Soc. Perkin Trans. I, 1986, 1865), Novikov, M. S. et al. (Tetrahedron Lett., 1997, 38, 4187), and Meyers, A. et al. (J. Amer. Chem. Soc., 1984, 106, 1146).

10

Example 55

As a specific embodiment of an oral composition of a compound of this invention, 100mg of one of the compounds described herein is formulated with sufficient
15 finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gel capsule.

Pharmacological Profiles of the Compounds in Cloned Human Adrenergic Receptors.

5 Binding affinities were measured for selected compounds of the invention at six cloned human alpha-1 and alpha-2 receptor subtypes, as well as at the L-type calcium channel. The protocols for these experiments are given below.

10 **Protocol for the Determination of the Potency of α_1 Antagonists**

The activity of compounds at the different human receptors was determined in vitro using cultured cell lines that selectively express the receptor of interest.
15 These cell lines were prepared by transfecting the cloned cDNA or cloned genomic DNA or constructs containing both genomic DNA and cDNA encoding the human α -adrenergic receptors as follows:

20 **α_{1D} Human Adrenergic Receptor:** The entire coding region of α_{1D} (1719 bp), including 150 base pairs of 5' untranslated sequence (5' UT) and 300 bp of 3' untranslated sequence (3' UT), was cloned into the BamHI and ClaI sites of the polylinker-modified eukaryotic
25 expression vector pCEXV-3, called EXJ.HR. The construct involved the ligation of partial overlapping human lymphocyte genomic and hippocampal cDNA clones: 5' sequence were contained on a 1.2 kb SmaI-XhoI genomic fragment (the vector-derived BamHI site was used for
30 subcloning instead of the internal insert-derived SmaI site) and 3' sequences were contained on an 1.3 kb XhoI-ClaI cDNA fragment (the ClaI site was from the vector polylinker). Stable cell lines were obtained by cotransfection with the plasmid $\alpha 1A/EXJ$ (expression

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vector containing the $\alpha 1A$ receptor gene (old nomenclature)) and the plasmid pGCcos3neo (plasmid containing the aminoglycoside transferase gene) into LM(tk-) cells using calcium phosphate technique. The
5 cells were grown, in a controlled environment (37°C., 5% CO₂), as monolayers in Dulbecco's modified Eagle's Medium (GIBCO, Grand Island, NY) containing 25mM glucose and supplemented with 10% bovine calf serum, 100 units/ml penicillin g, and 100 μ g/ml streptomycin
10 sulfate. Stable clones were then selected for resistance to the antibiotic G-418 (1 mg/ml), and membranes were harvested and assayed for their ability to bind [³H]prazosin as described below (see "Radioligand Binding assays").

15 The cell line expressing the human α_{1D} receptor used herein was designated L- α_{1A} (old nomenclature) and was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A.
20 under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. The cell line expressing the human α_{1D} receptor, was accorded ATCC Accession No. CRL 11138, and was deposited
25 on September 25, 1992.

α_{1B} Human Adrenergic Receptor: The entire coding region of $\alpha 1B$ (1563 bp), including 200 base pairs and 5' untranslated sequence (5' UT) and 600 bp of 3'
30 untranslated sequence (3' UT), was cloned into the EcoRI site of pCEXV-3 eukaryotic expression vector. The construct involved ligating the full-length containing EcoRI brainstem cDNA fragment from λ ZapII into the expression vector. Stable cell lines were selected as

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- described above. The cell line used herein was designated L- α_{1B} and was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions
- 5 of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. The cell line L- α_{1B} was accorded ATCC Accession No. CR 11139, on September 29, 1992.
- 10 **α_{1A} Human Adrenergic Receptor:** The entire coding region of α_{1A} (1401 bp), including 400 base pairs of 5' untranslated sequence (5' UT) and 200 bp of 3' untranslated sequence (3' UT), was cloned into the KpnI site of the polylinker-modified pCEXV-3-derived
- 15 eukaryotic expression vector, EXJ.RH. The construct involved ligating three partial overlapping fragments: a 5' 0.6kb HincII genomic clone, a central 1.8 EcoRI hippocampal cDNA clone, and a 3' 0.6Kb PstI genomic clone. The hippocampal cDNA fragment overlaps with the
- 20 5' and 3' genomic clones so that the HincII and PstI sites at the 5' and 3' ends of the cDNA clone, respectively, were utilized for ligation. This full-length clone was cloned into the KpnI site of the expression vector, using the 5' and 3' KpnI sites of the
- 25 fragment, derived from vector (i.e., pBluescript) and 3'-untranslated sequences, respectively. Stable cell lines were selected as described above. The stable cell line expressing the human α_{1A} receptor used herein was designated L- α_{1C} (old nomenclature) and was deposited
- 30 with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure.

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The cell line expressing the human α_{1A} receptor was accorded Accession No. CR 11140, on September 25, 1992.

Radioligand Binding Assays: Transfected cells from
5 culture flasks were scraped into 5ml of 5mM Tris-HCl,
5mM EDTA, pH 7.5, and lysed by sonication. The cell
lysates were centrifuged at 1000 rpm for 5 min at 4°C,
and the supernatant was centrifuged at 30,000 x g for 20
min at 4°C. The pellet was suspended in 50mM Tris-HCl,
10 1mM MgCl₂, and 0.1% ascorbic acid at pH 7.5. Binding of
the α_1 antagonist [³H]prazosin (0.5 nM, specific
activity 76.2 Ci/mmol) to membrane preparations of
LM(tk-) cells was done in a final volume of 0.25 ml and
incubated at 37°C for 20 min. Nonspecific binding was
15 determined in the presence of 10 μ M phentolamine. The
reaction was stopped by filtration through GF/B filters
using a cell harvester. Inhibition experiments,
routinely consisting of 7 concentrations of the tested
compounds, were analyzed using a non-linear regression
20 curve-fitting computer program to obtain K_i values.

α_2 Human Adrenergic Receptors: To determine the potency
of α_1 antagonists at the α_2 receptors, LM(tk-) cell
lines stably transfected with the genes encoding the
25 α_{2A} , α_{2B} , and α_{2C} receptors were used. The cell line
expressing the α_{2A} receptor is designated L- α_{2A} , and was
deposited on November 6, 1992 under ATCC Accession No.
CRL 11180. The cell line expressing the α_{2B} receptor is
designated L-NGC- α_{2B} , and was deposited on October 25,
30 1989 under ATCC Accession No. CRL10275. The cell line
expressing the α_{2C} receptor is designated L- α_{2C} , and was
deposited on November 6, 1992 under ATCC Accession No.
CRL-11181. All the cell lines were deposited with the
American Type Culture Collection, 12301 Parklawn Drive,

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Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. Cell lysates were prepared as
5 described above (see Radioligand Binding Assays), and suspended in 25 mM glycylglycine buffer (pH 7.6 at room temperature). Equilibrium competition binding assay were performed using [3H]rauwolscine (0.5nM), and nonspecific binding was determined by incubation with
10 10 μ M phentolamine. The bound radioligand was separated by filtration through GF/B filters using a cell harvester.

15 **Determination of the Activity of α_1 Antagonists at Calcium Channels**

The potency of α_1 antagonists at calcium channels may be determined in competition binding assays of [3H]nitrendipine to membrane fragments of rat cardiac muscle, essentially as described by Glossman and Ferry
20 (Methods in Enzymology 109:513-550, 1985). Briefly, the tissue is minced and homogenized in 50mM Tris-HCl (pH 7.4) containing 0.1mM phenylmethylsulfonyl fluoride. The homogenates are centrifuged at 1000 g for 15 minutes, and the resulting supernatant centrifuged at
25 45,000 g for 15 minutes. The 45,000 g pellet is suspended in buffer and centrifuged a second time. Aliquots of membrane protein are then incubated for 30 minutes at 37°C in the presence of [3H]nitrendipine (1 nM), and nonspecific binding determined in the presence
30 of 10 μ M nifedipine. The bound radioligand is separated by filtration through GF/B filters using a cell harvester.

The compounds described above were assayed using cloned
35 human alpha adrenergic receptors. The preferred

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compounds were found to be selective α_{1A} antagonists. The binding affinities of several compounds are illustrated in the following table.

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Binding affinities of selected compounds of the present invention at cloned human α_{1D} , α_{1B} and α_{1A} receptors.

5

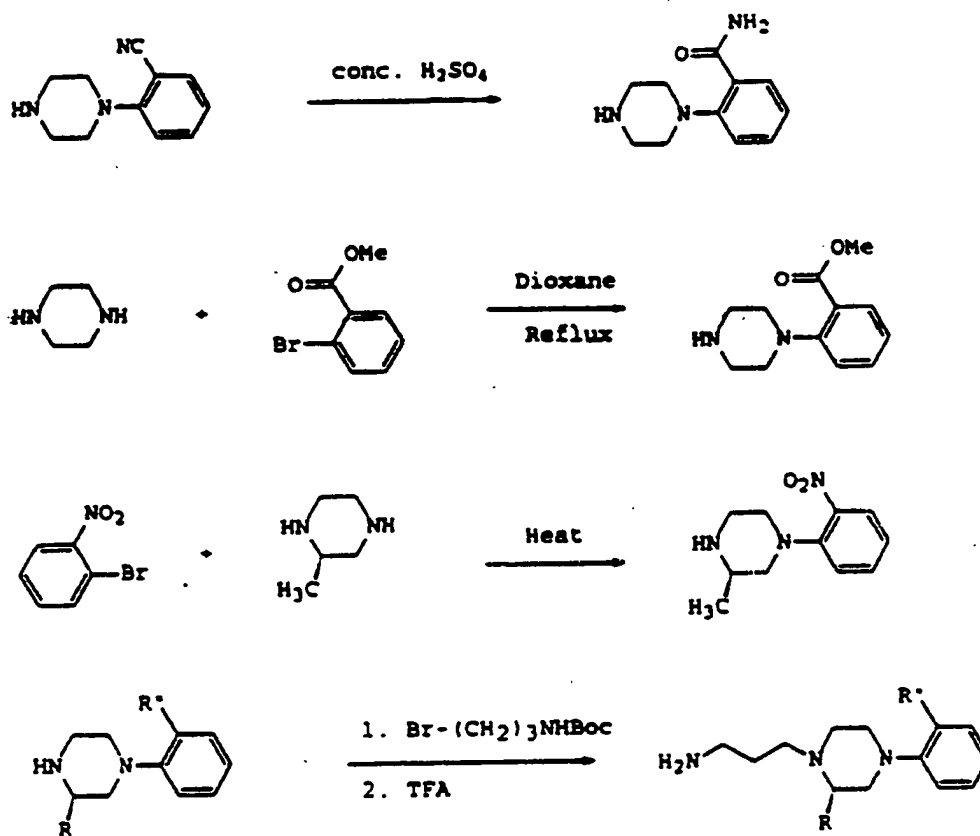
Example	$h\alpha_{1D}$	$h\alpha_{1B}$	$h\alpha_{1A}$
	K_i	K_i	K_i
2	11	21	0.5
21	2455	891	21
28	3660	4012	0.7

10

h = human

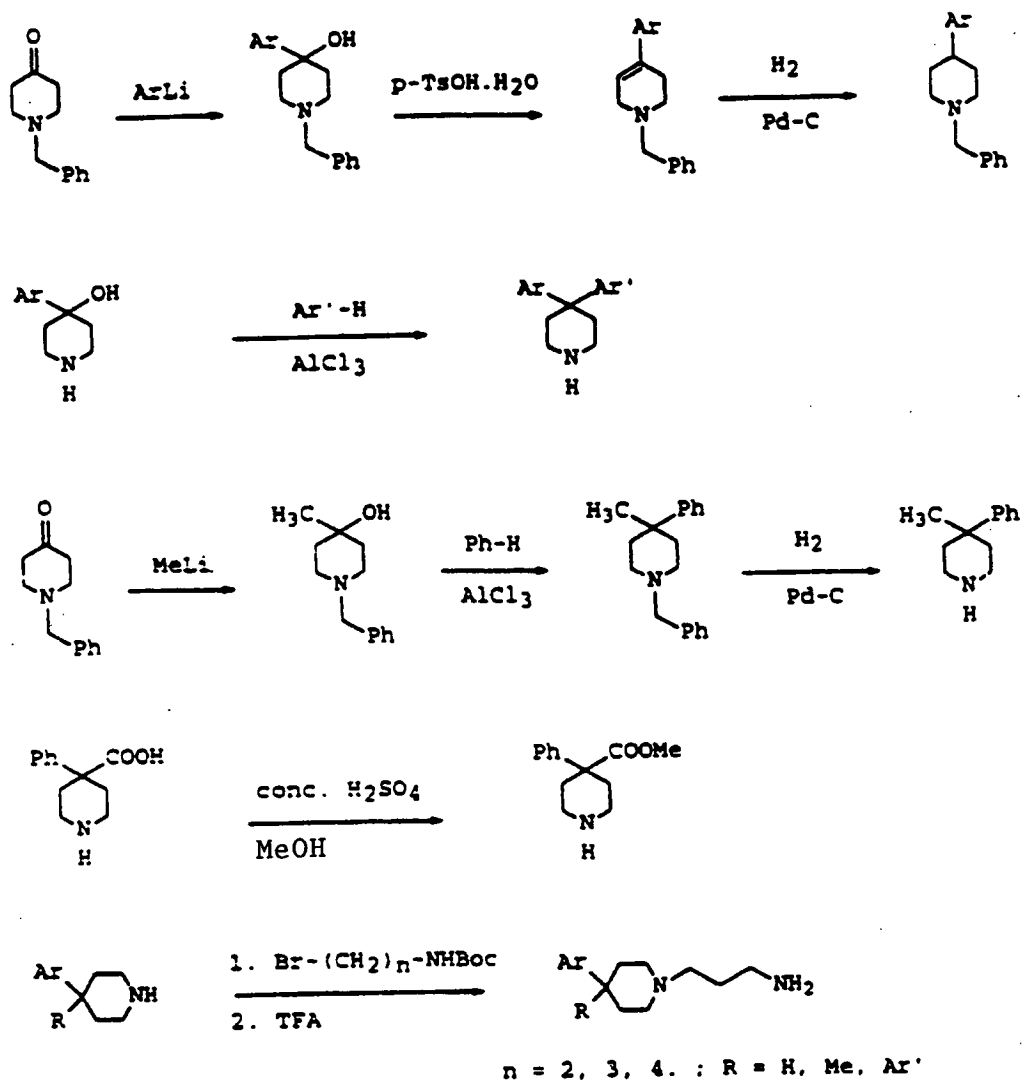
-170-

Scheme 1



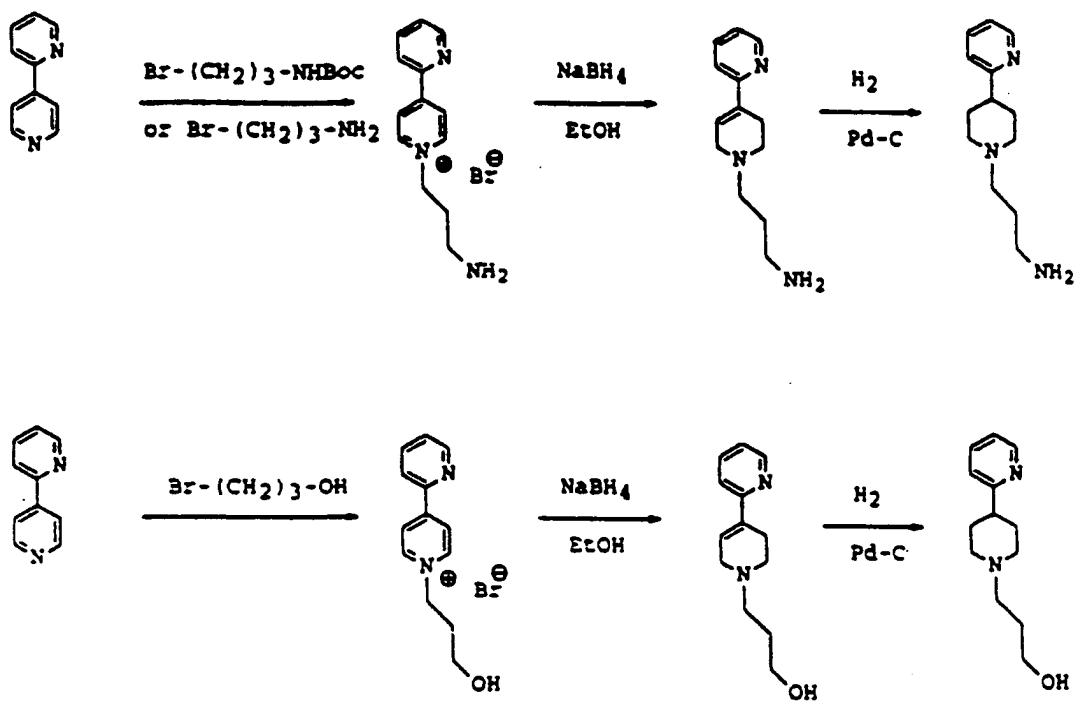
Scheme 1: General Synthesis of Piperazine side chains

Scheme 2



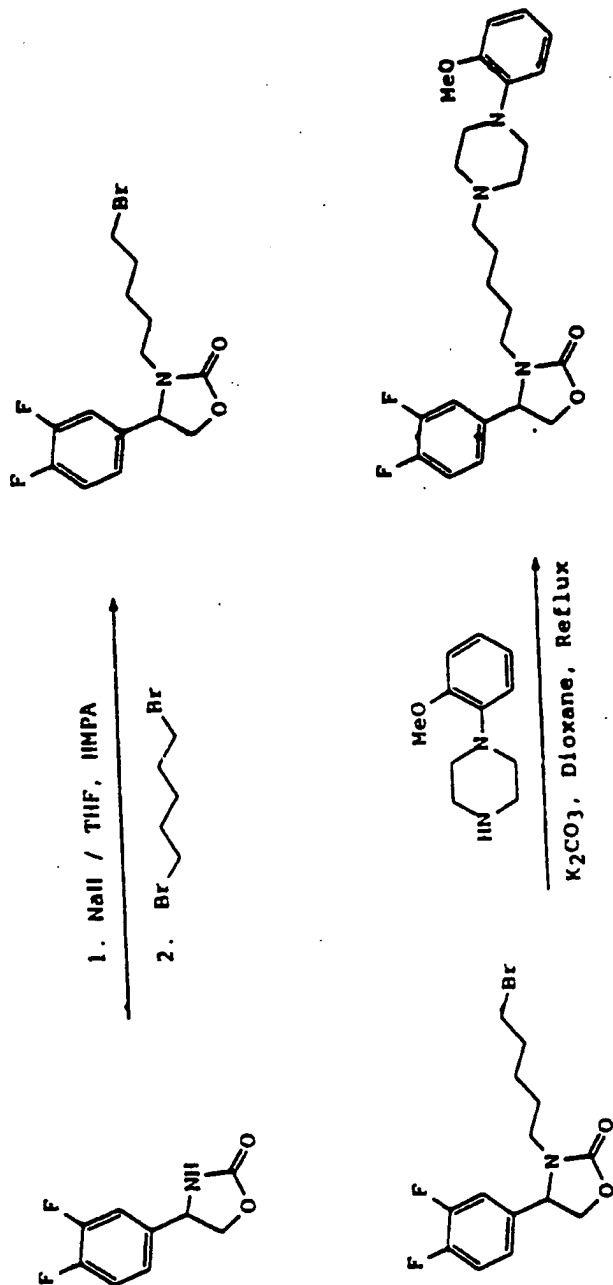
Scheme 2: General Synthesis of Piperidine Side Chains

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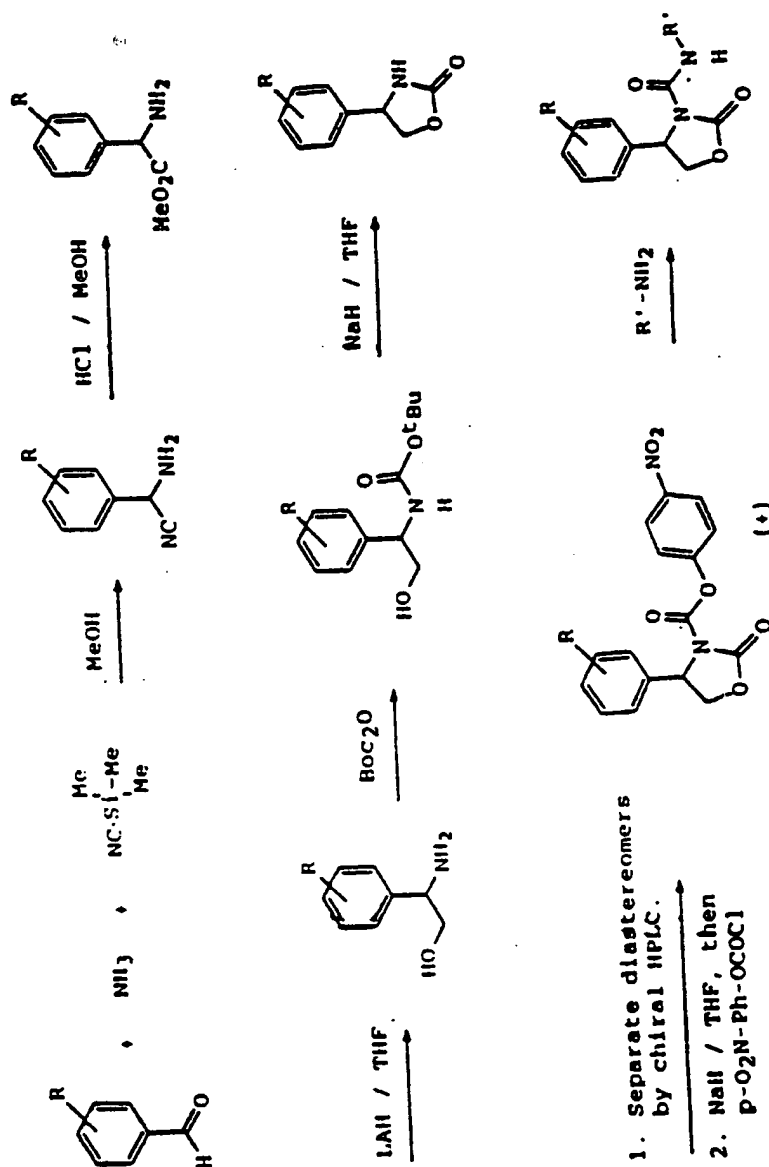
Scheme 3: Synthesis of Pyridyl piperidine containing side chains

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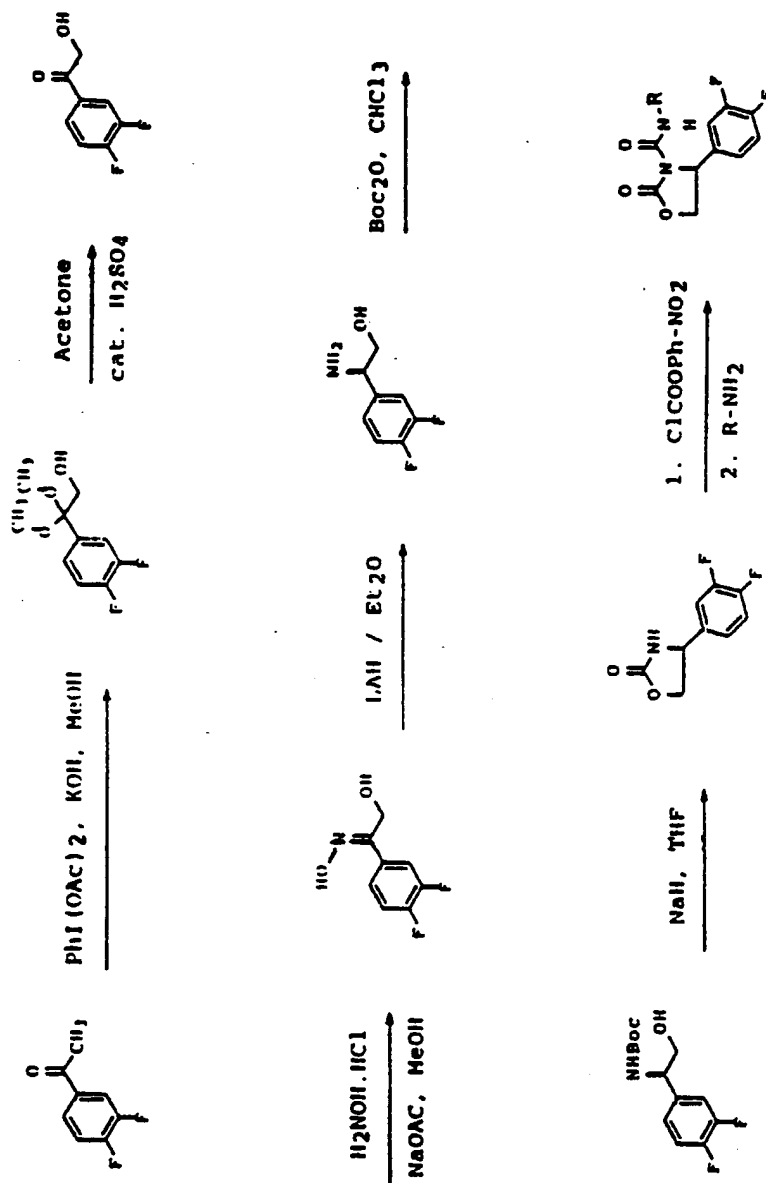
Scheme 4: Preparation of Example 2.

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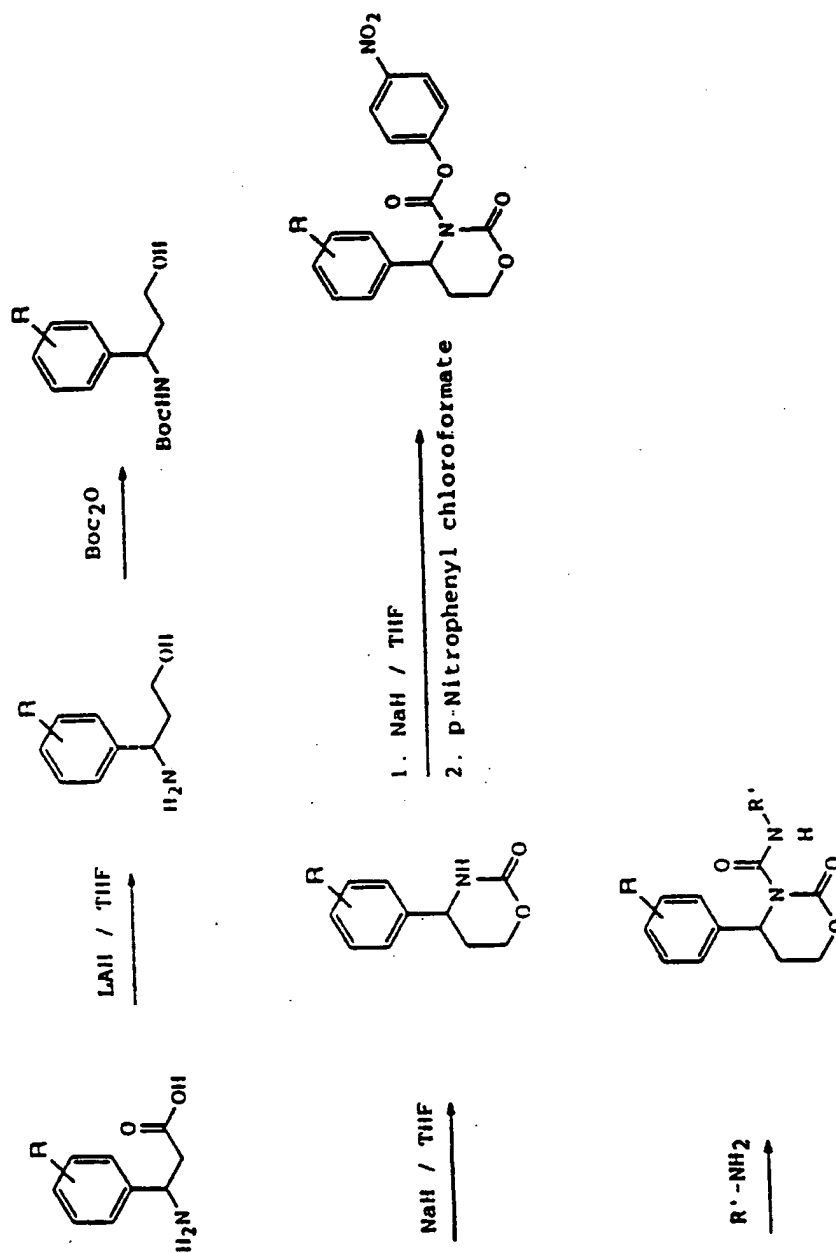
Scheme 3: General Synthesis of Oxazolidinones (Examples 1, 3, 6, 7, 8, 10, 14 and 22).

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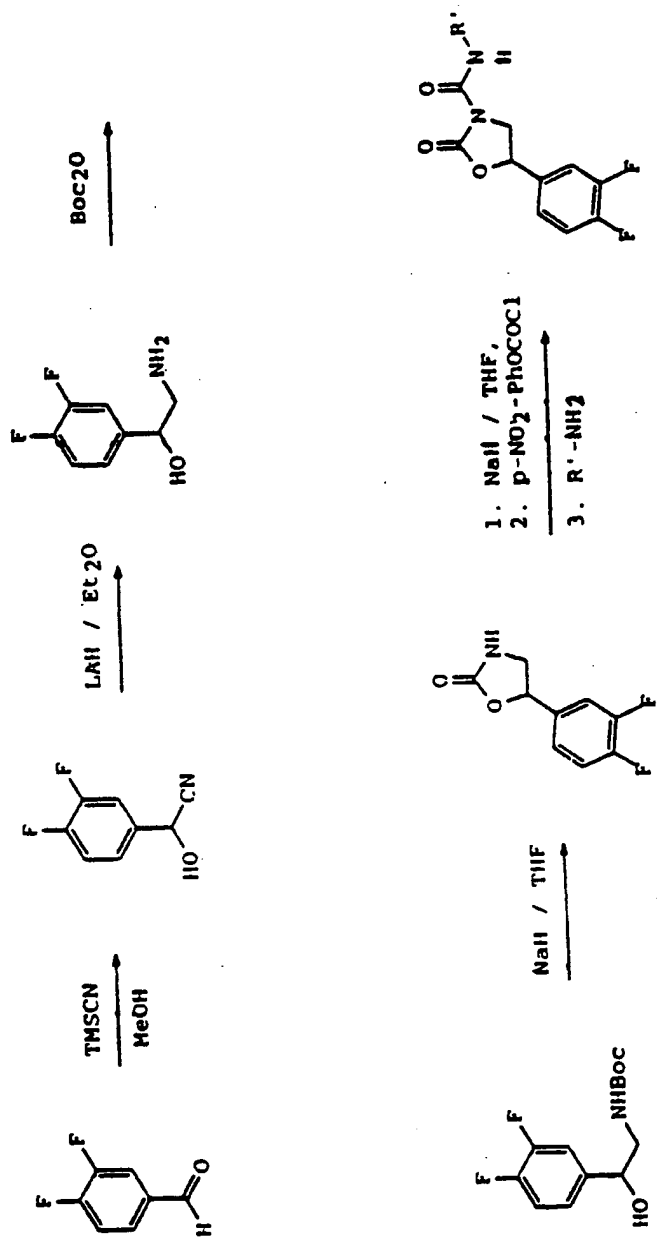


Scheme 6: Alternate Synthesis of Oxazolidinones described in Scheme 5.

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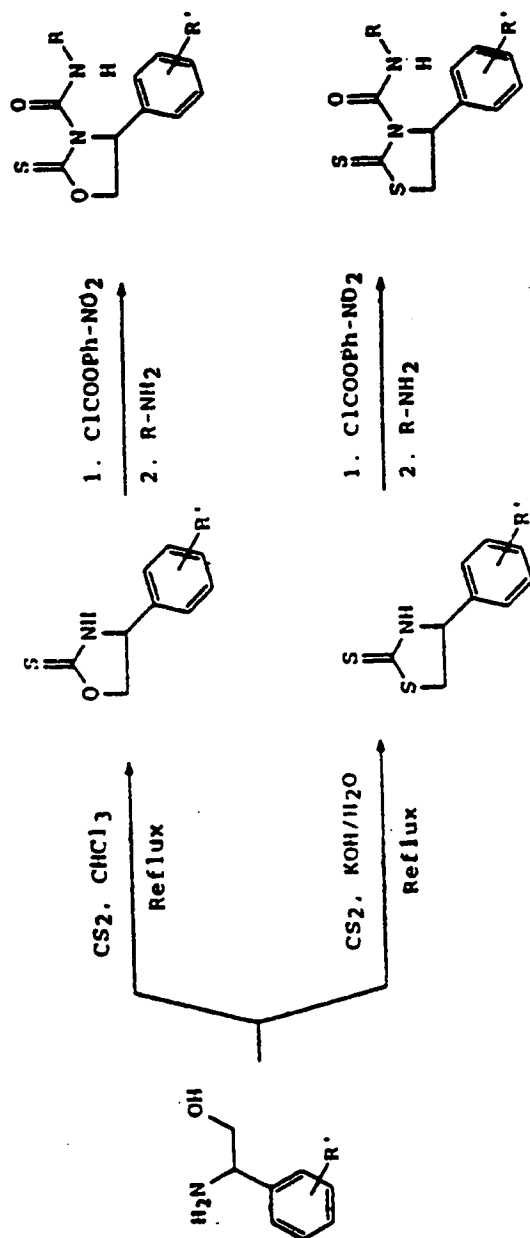
**Scheme 7:** General Synthesis of Oxazinones (Example 4)

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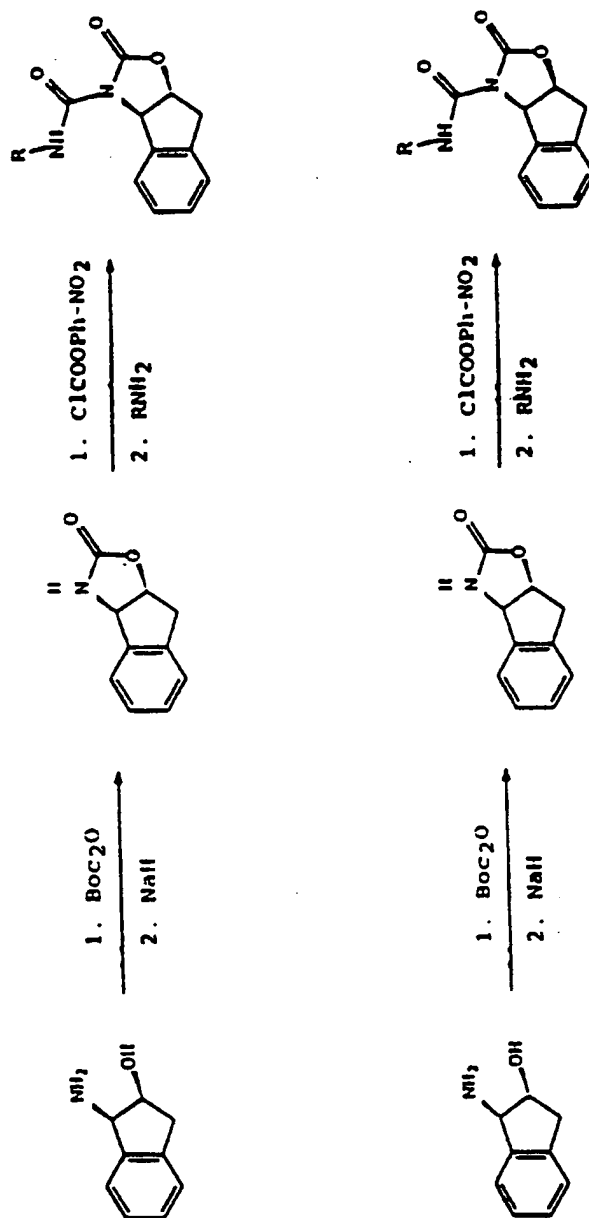


Scheme 8: Synthesis of Regioisomeric Oxazolidinones (Example 9).

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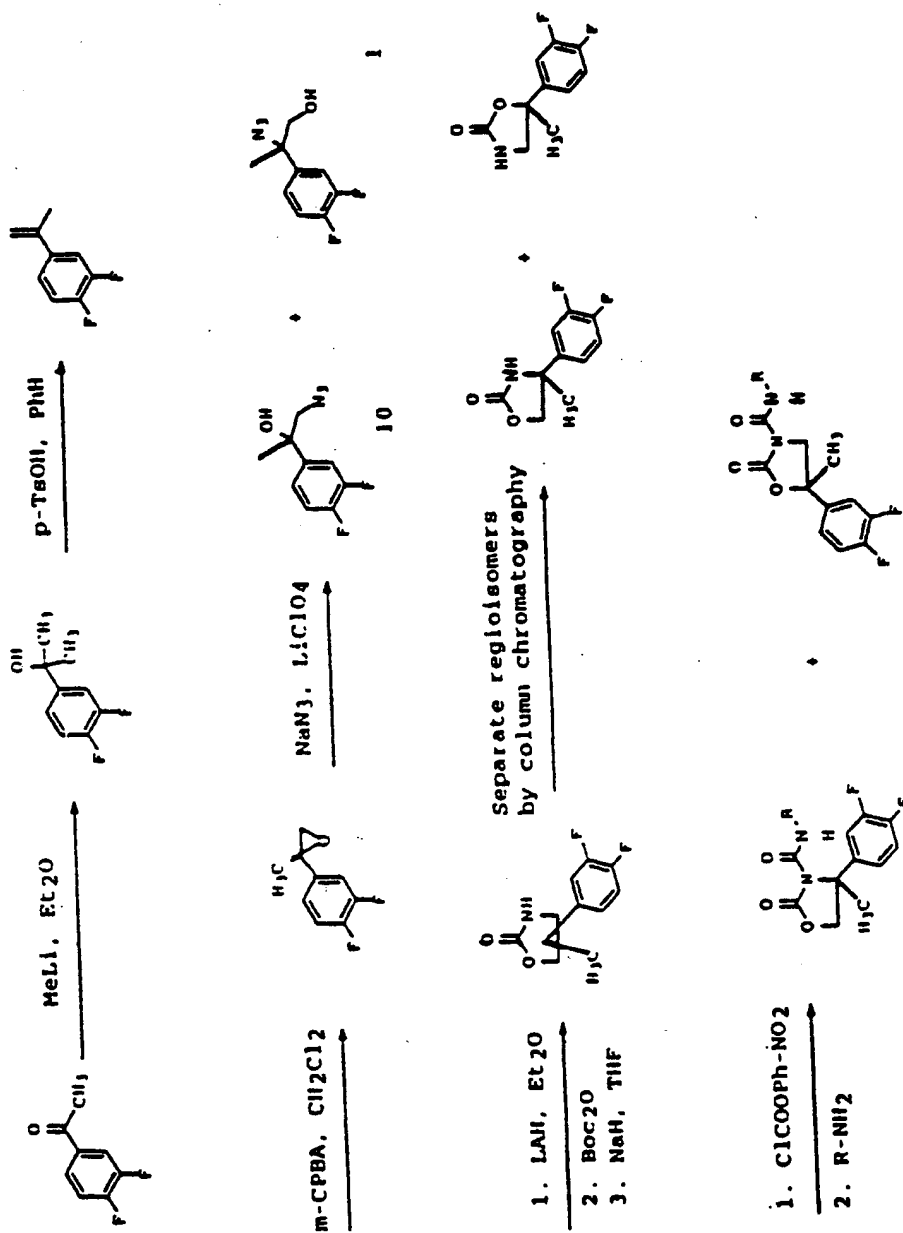
**Scheme 9: Synthesis of Oxazolidin-thione and Thiazolidin-thione (Examples 11, 12).**

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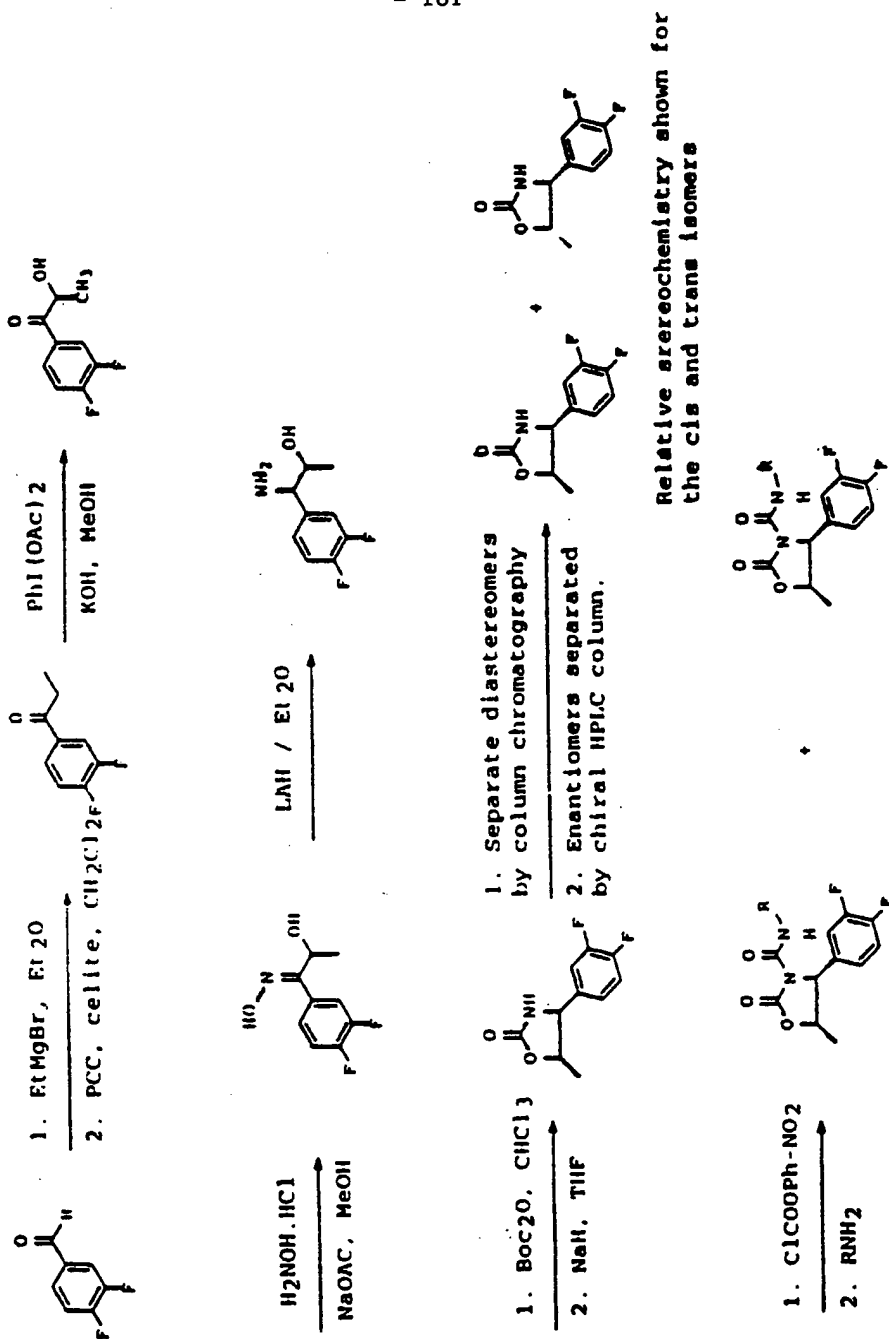
Scheme 10: General Synthesis for Example 13.

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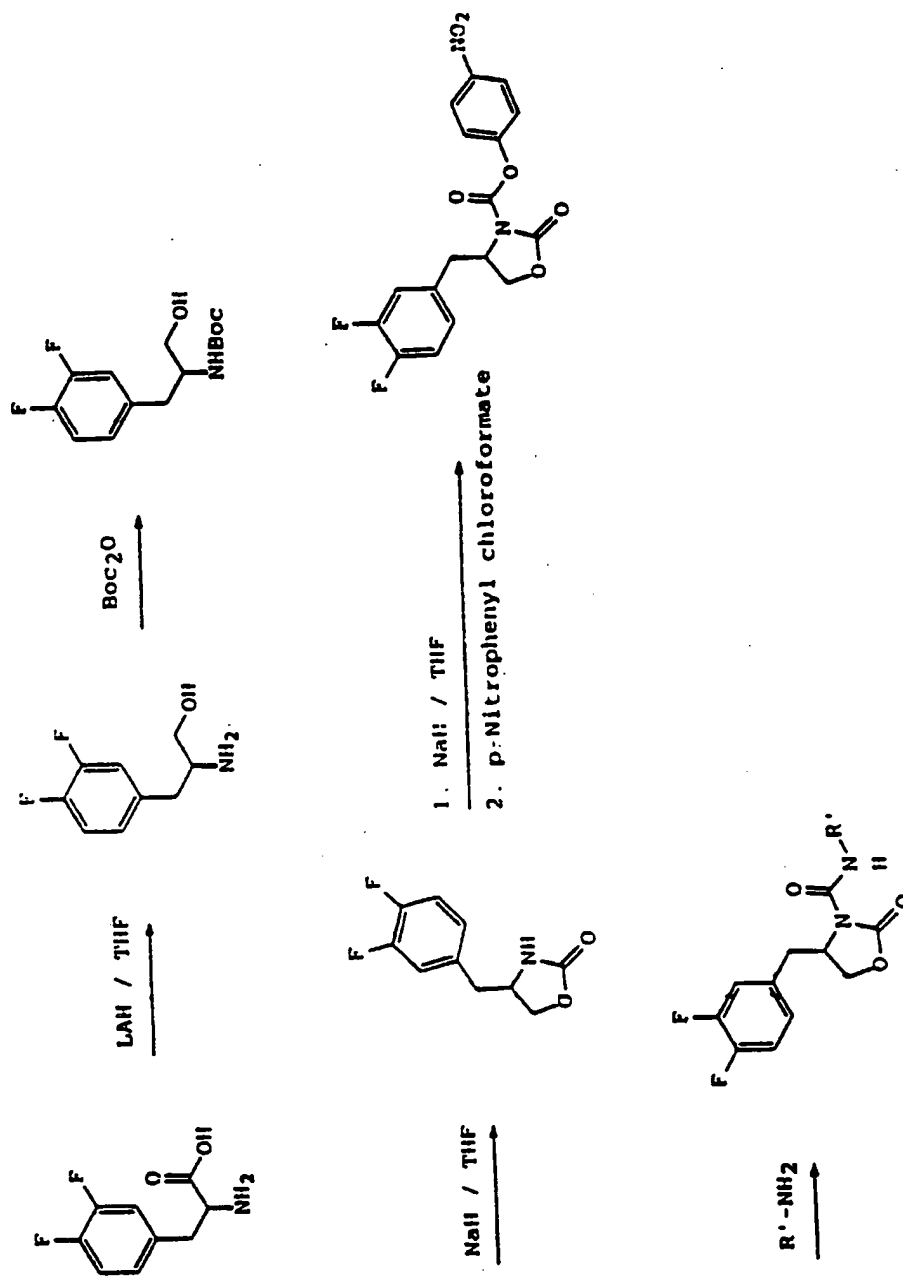
Scheme 11: Synthesis of Methylated Oxazolidinones (Examples 16, 17).

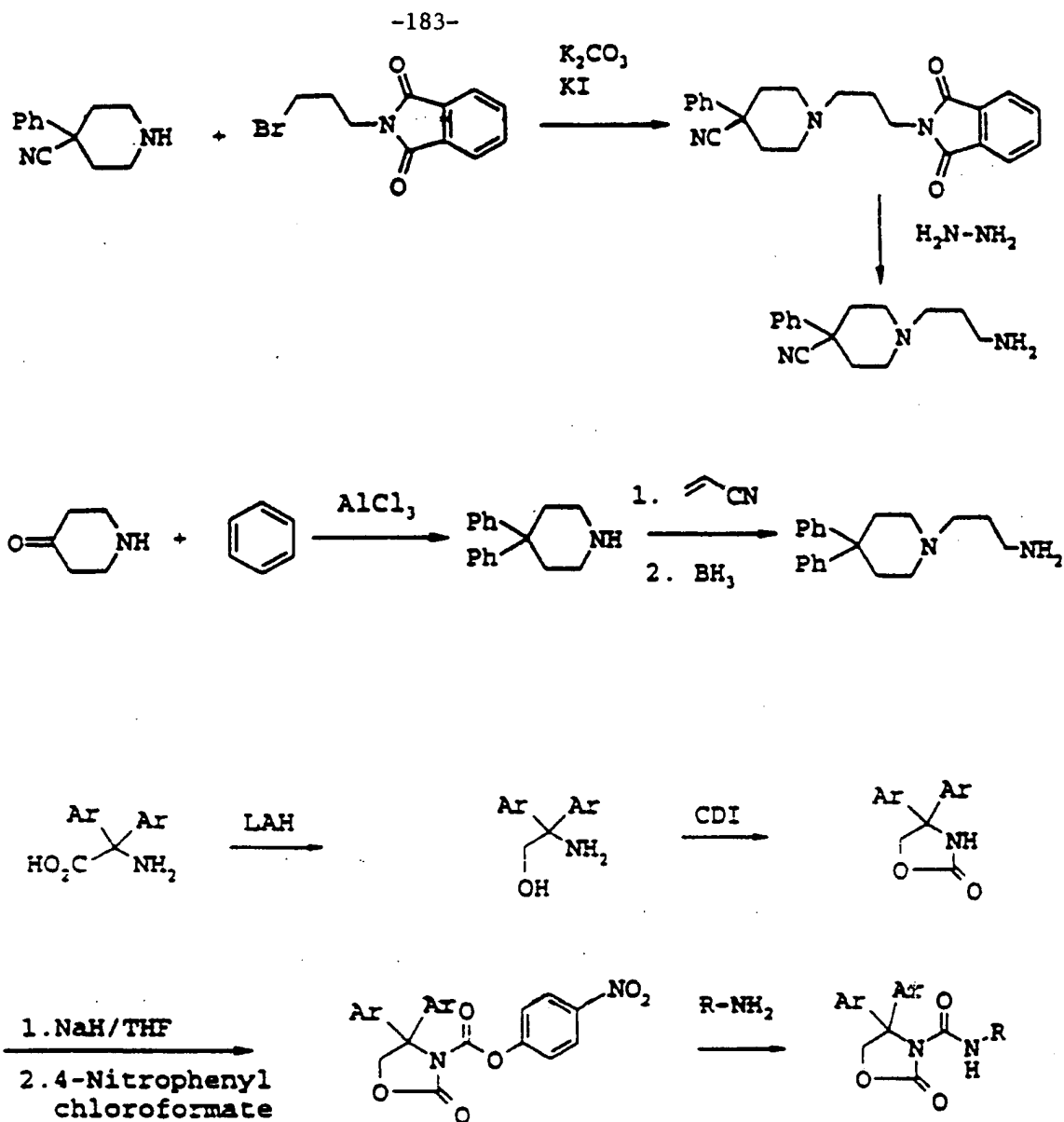
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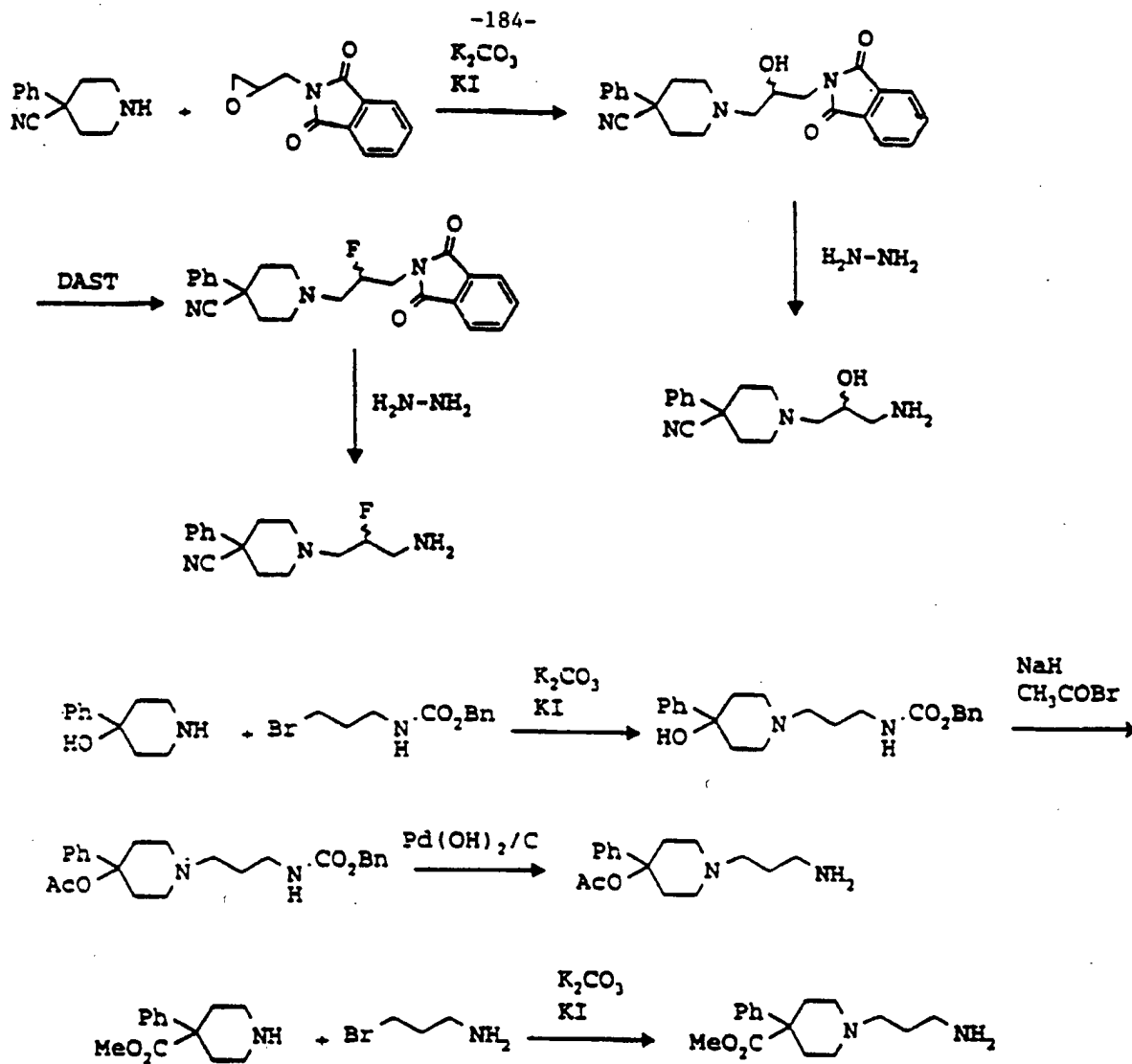
Scheme 12: Synthesis of Methylated Oxazolidinones (Examples 18, 19).

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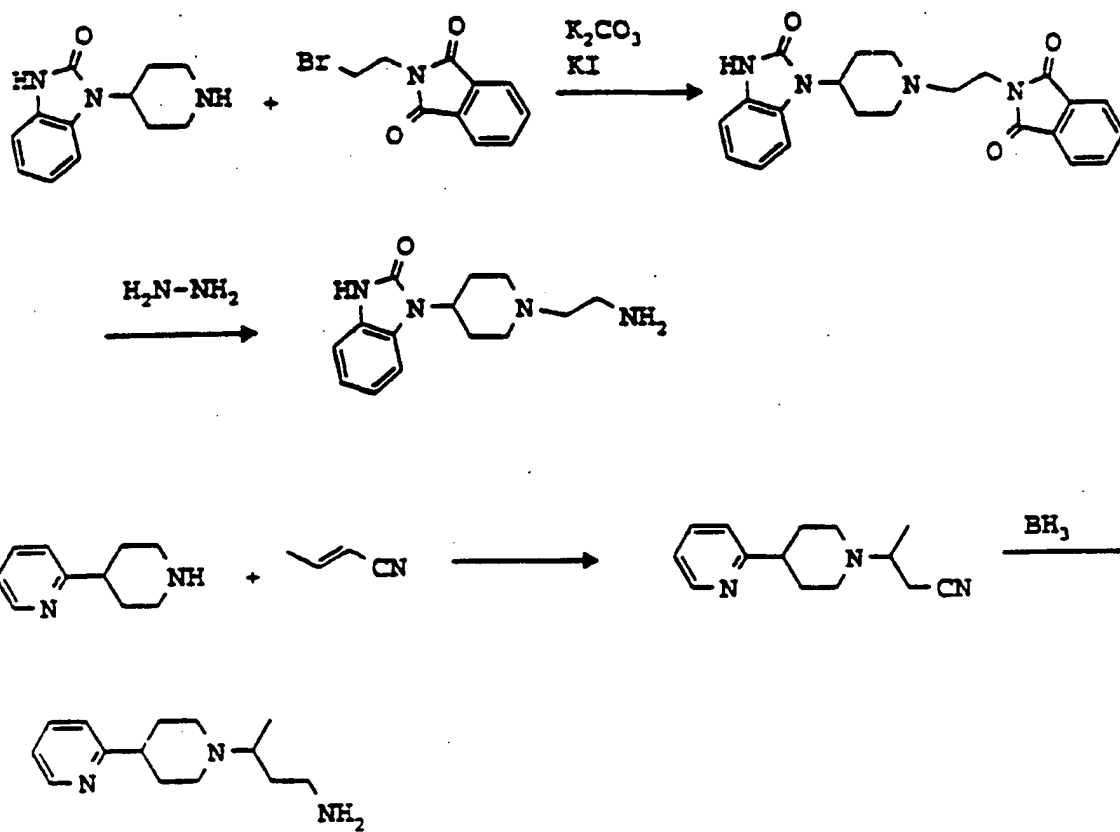
**Scheme 13:** General Synthesis of Benzyl Oxazolidinones (Example 20).



Scheme 14. Preparation of Examples 23 and 24

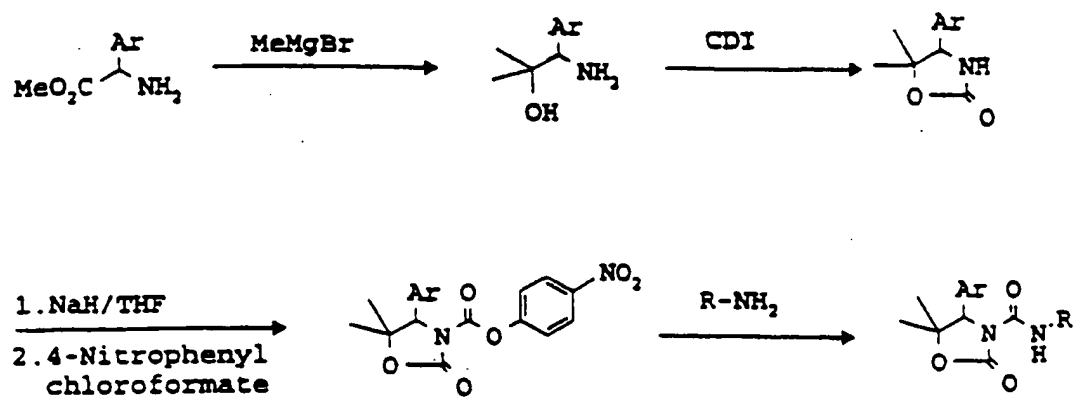


Scheme 15. Preparation of Side Chains

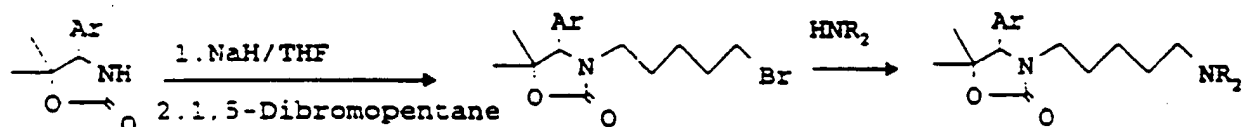


Scheme 16. Preparation of Side Chains (contd.).

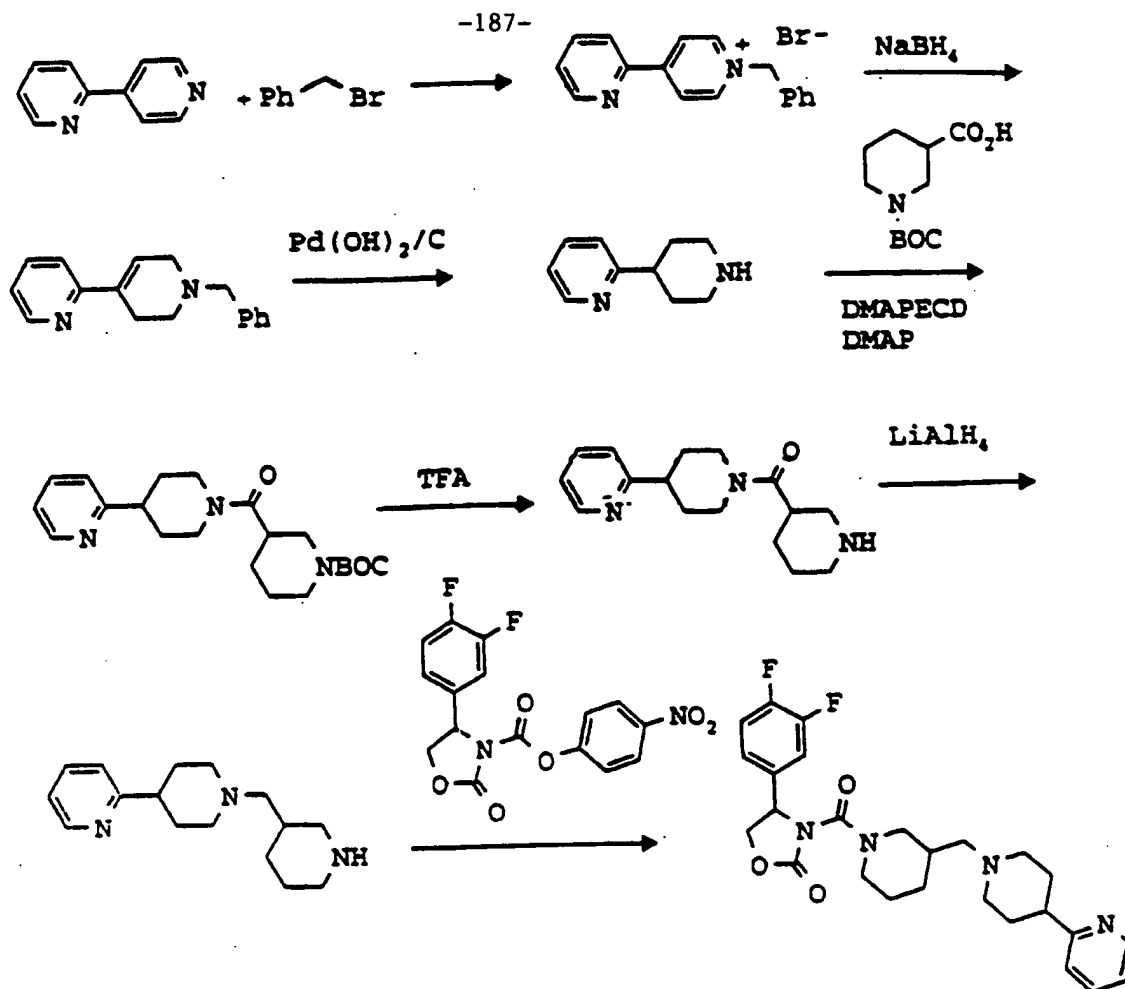
-186-



Scheme 17. Preparation of Examples 25-29 and 31.

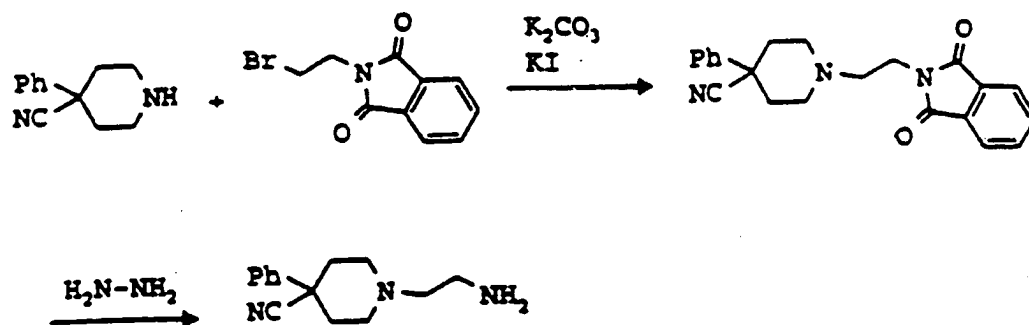


Scheme 18. Preparation of Example 30.

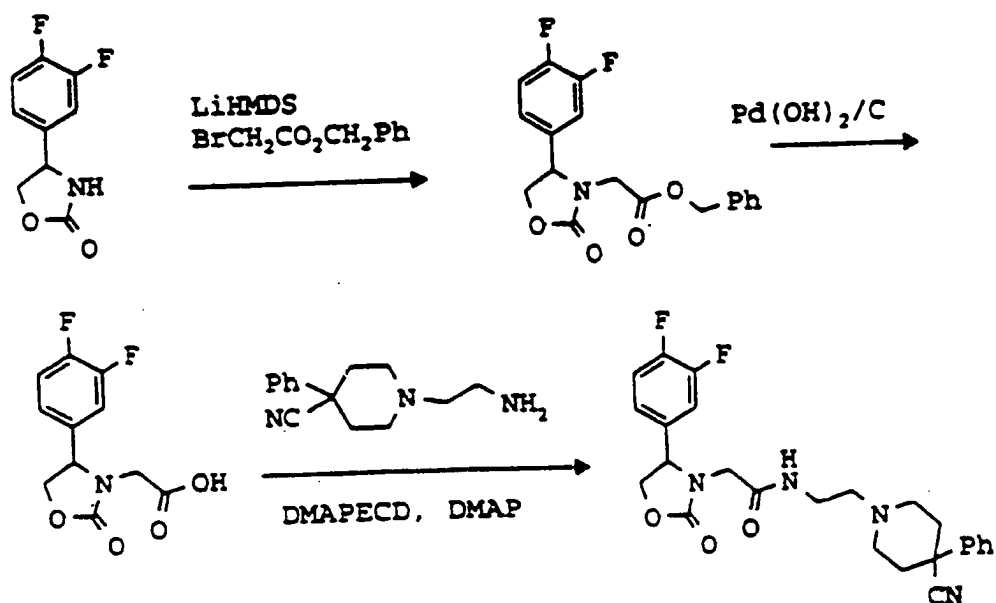


Scheme 19: Preparation of Example 32

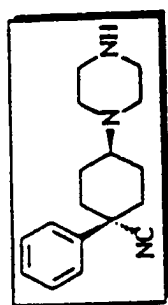
-188-



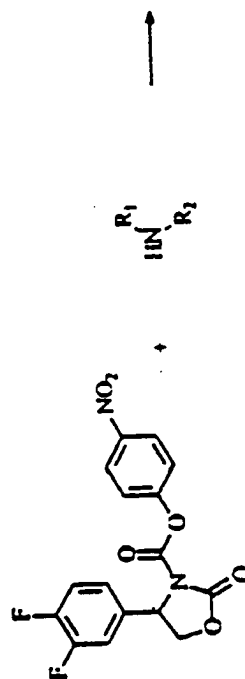
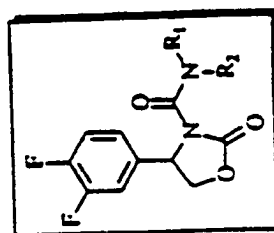
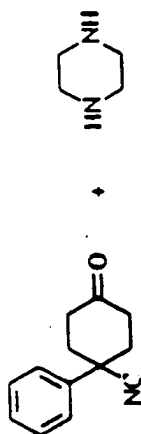
Scheme 20: Preparation of Side Chain



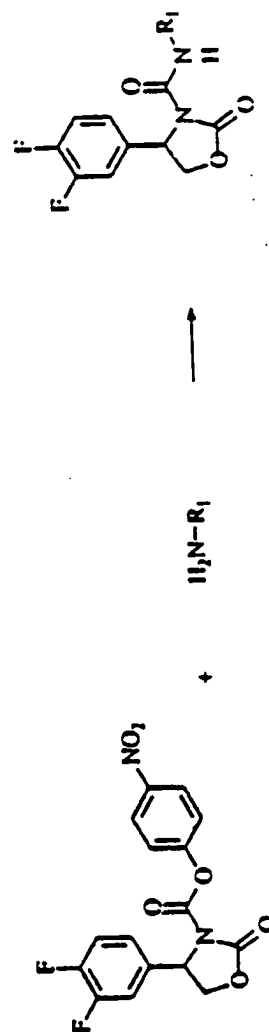
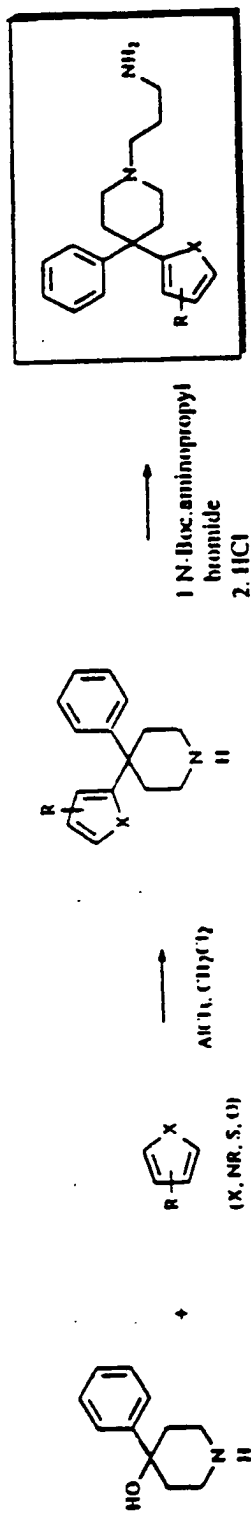
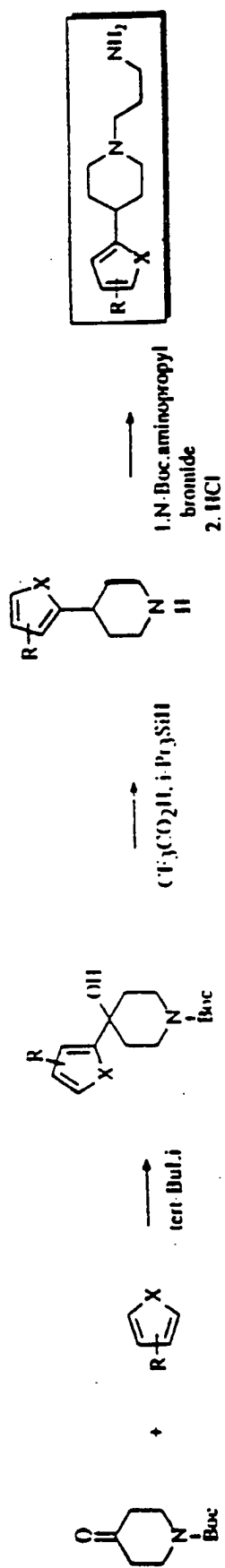
Scheme 21: Preparation of Example 33



1. TsOH, Reflux, PhMe
2. NaBH₄, EtOH

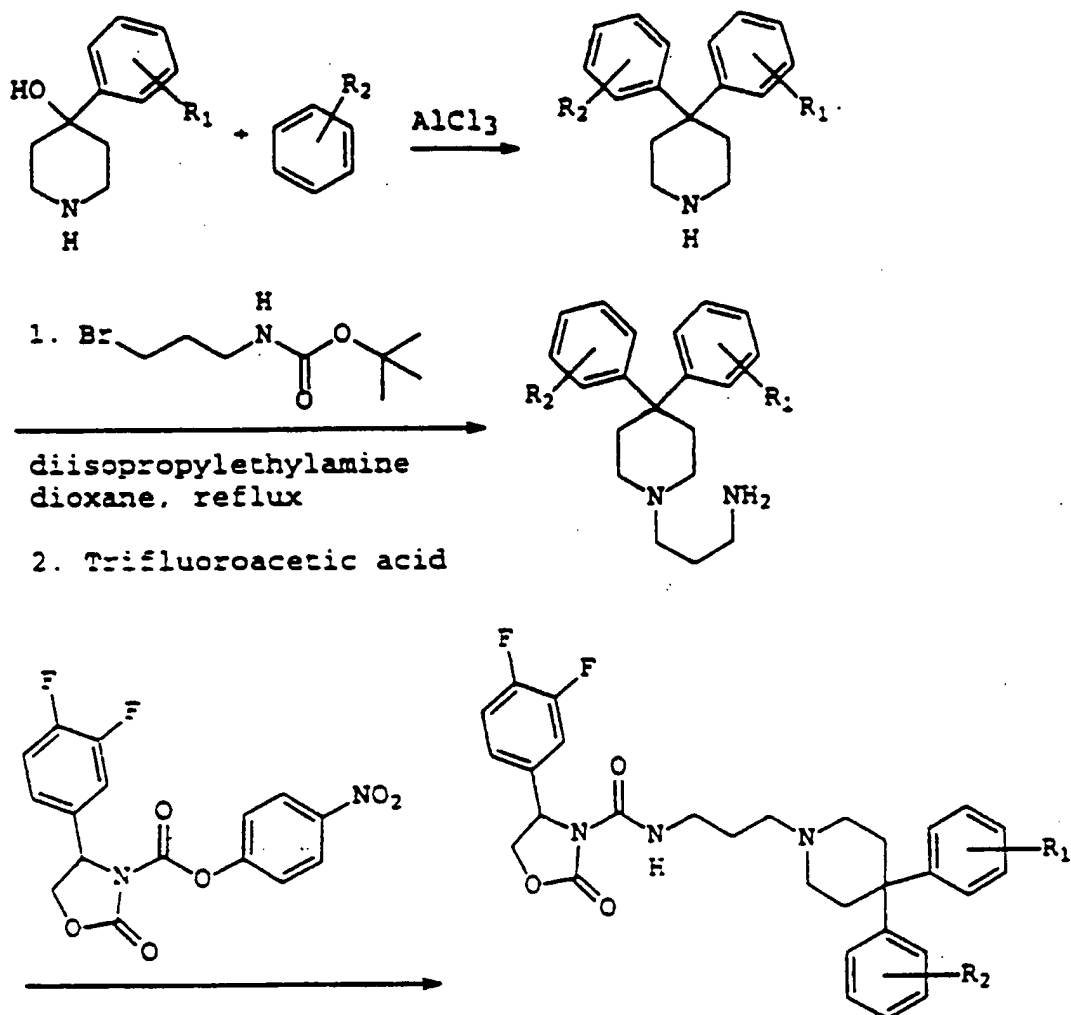


Scheme 22: Preparation of example 34

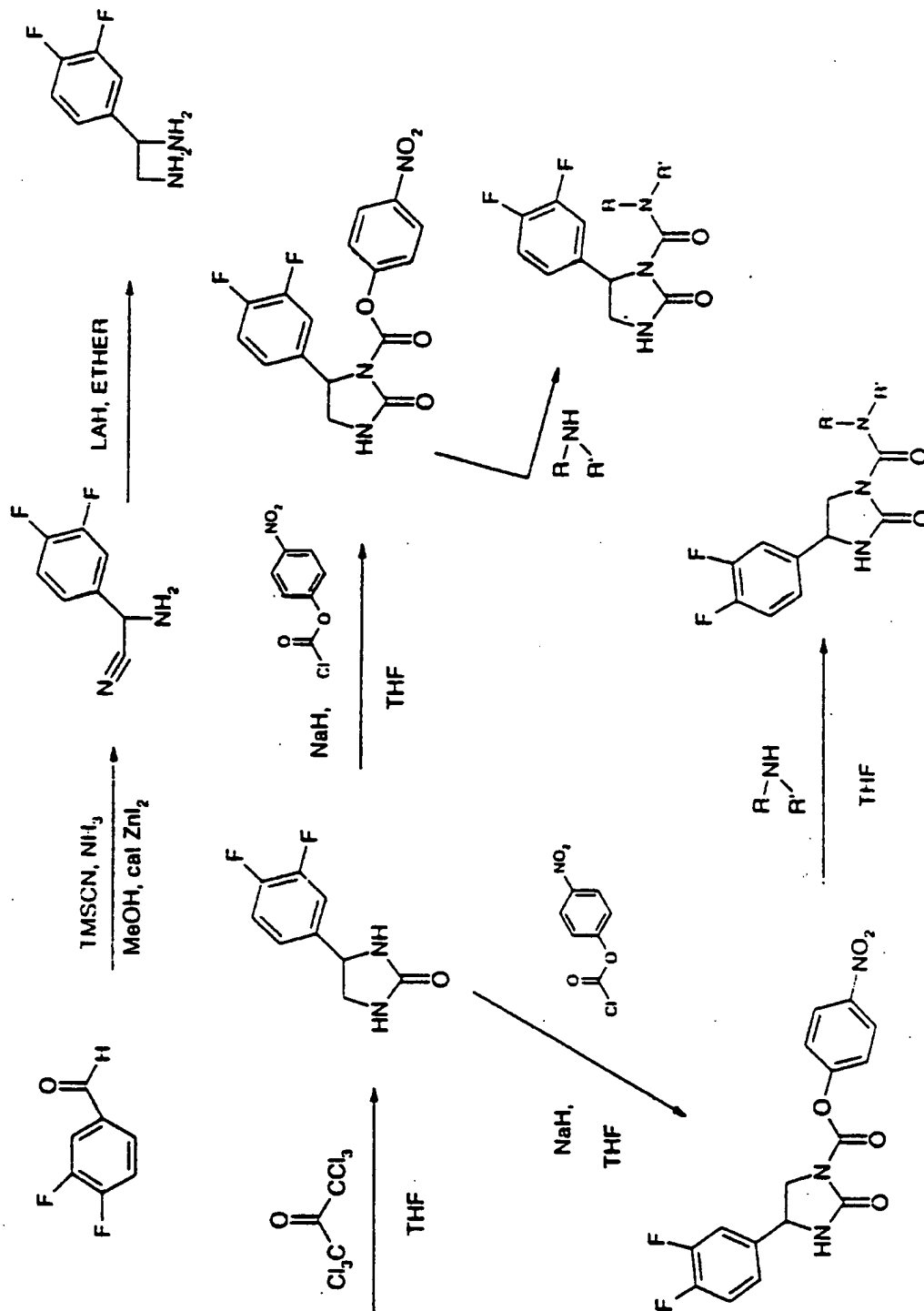


Scheme 23: Preparation of examples 35, 36 and 37

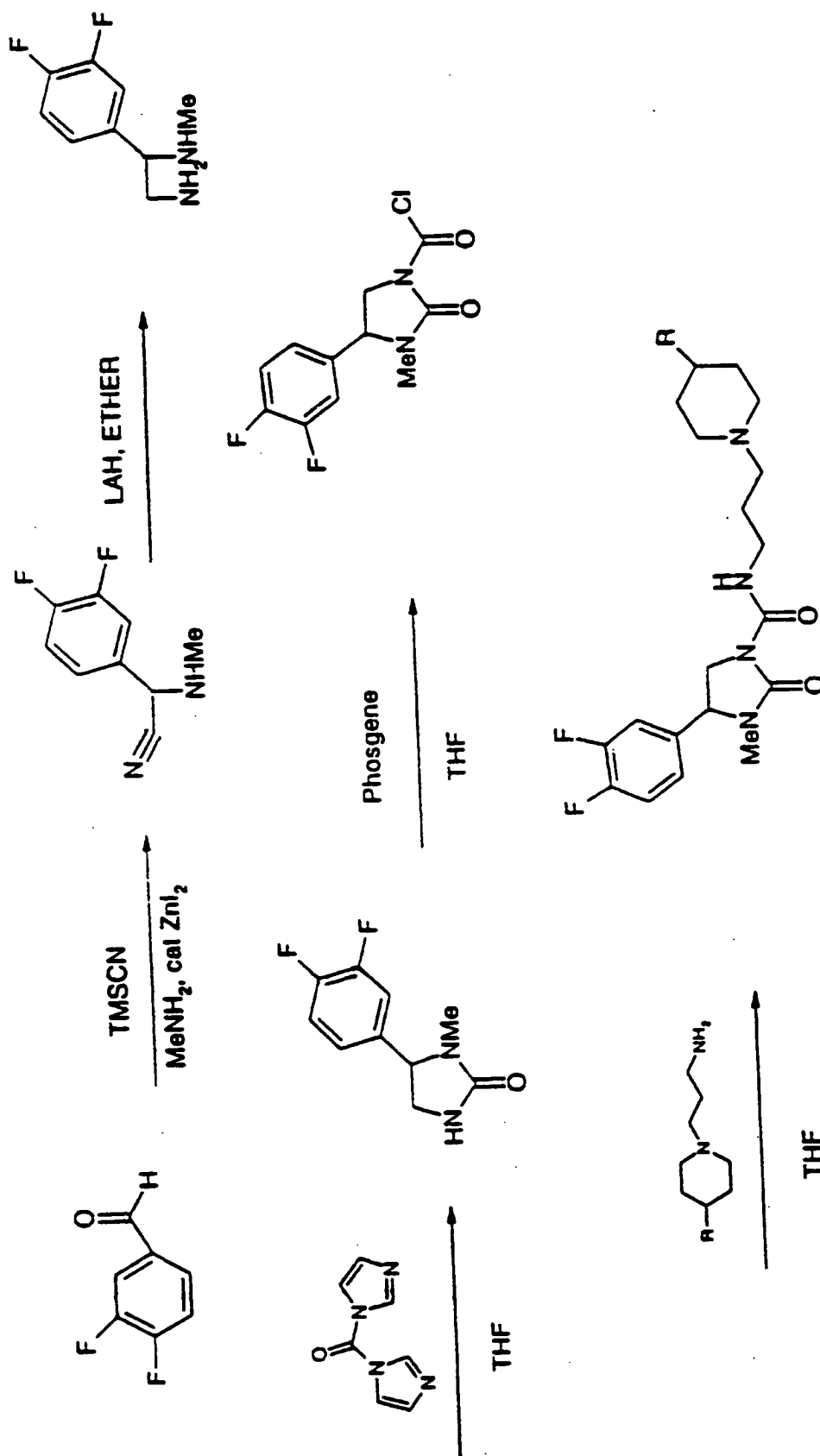
-191-



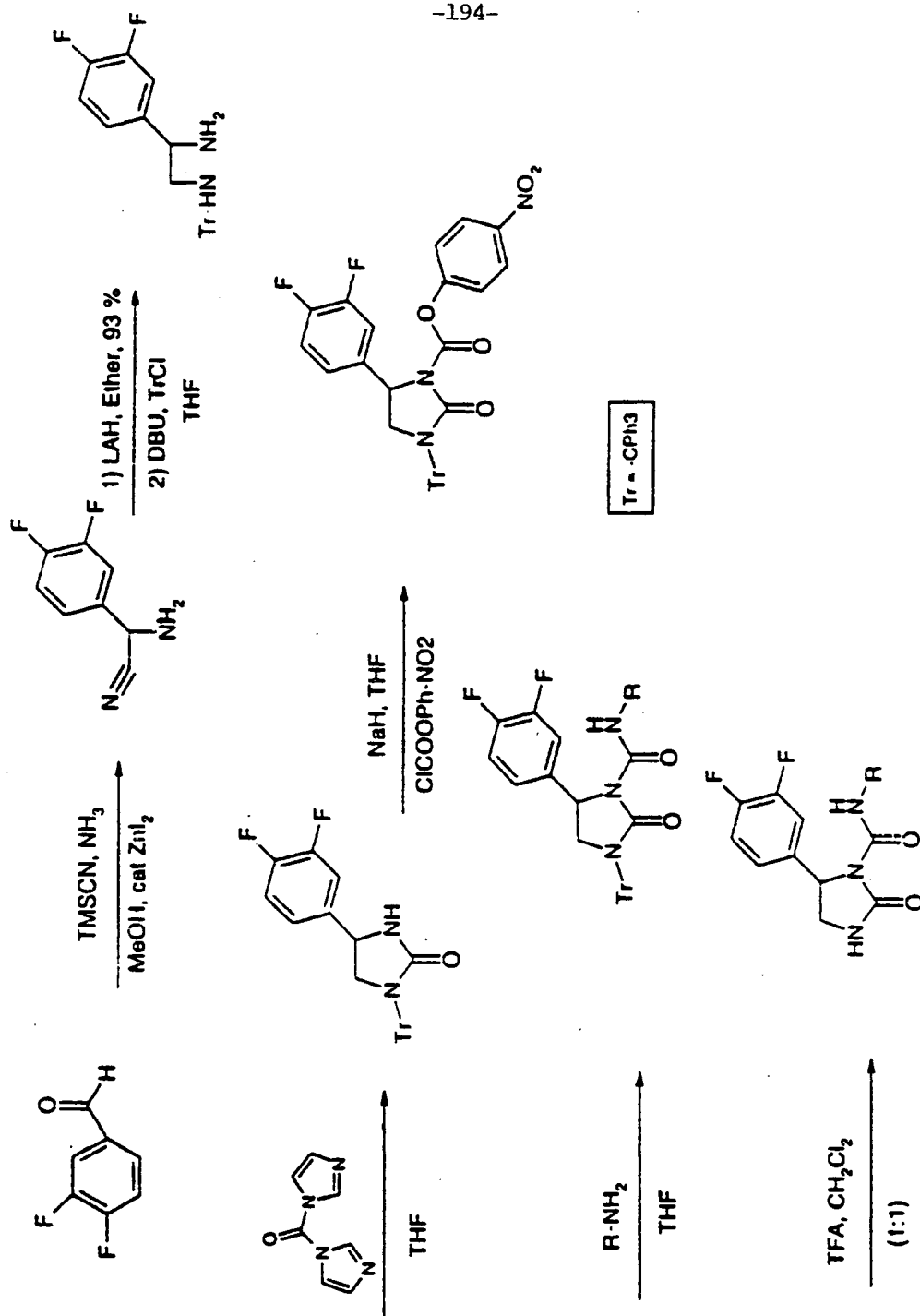
Scheme 24 : Preparation of Examples 38-42



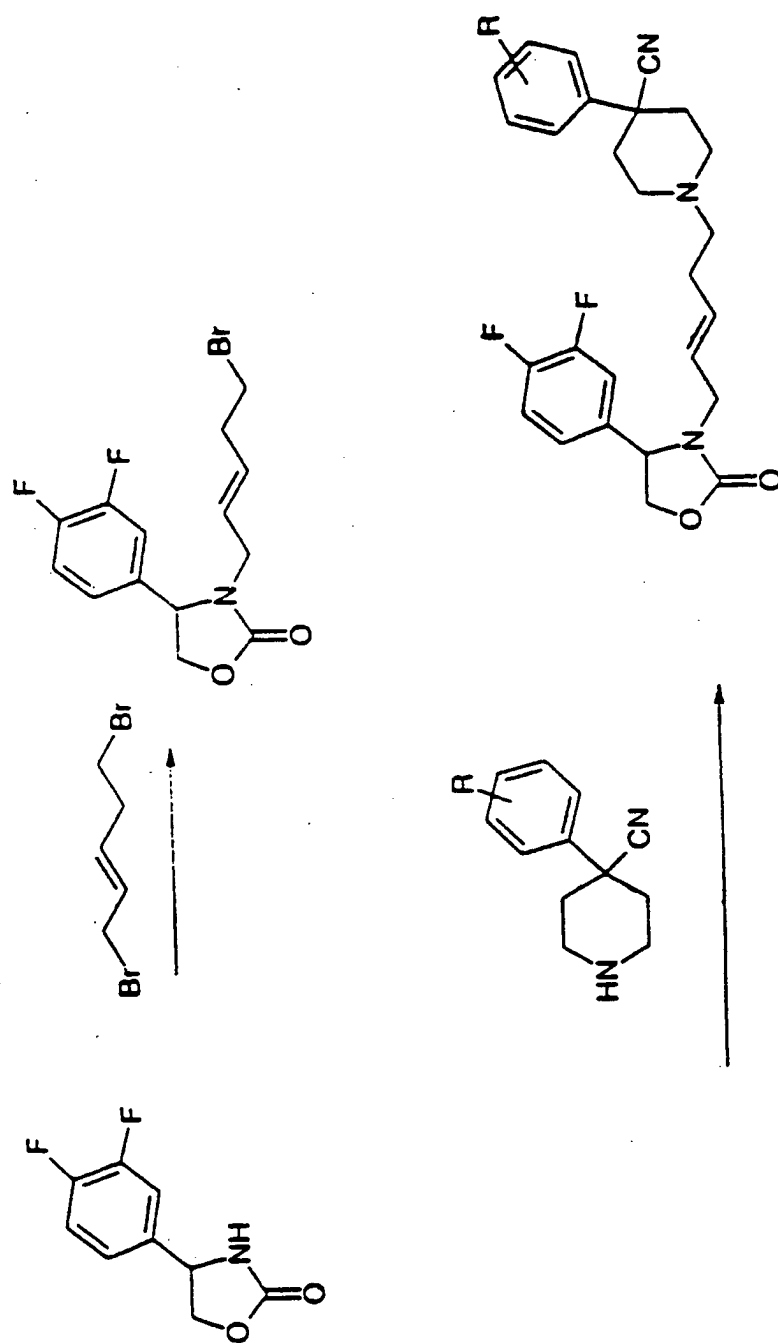
Scheme 25: Preparation of Examples 43 and 44.



Scheme 26: Preparation of Example 45.

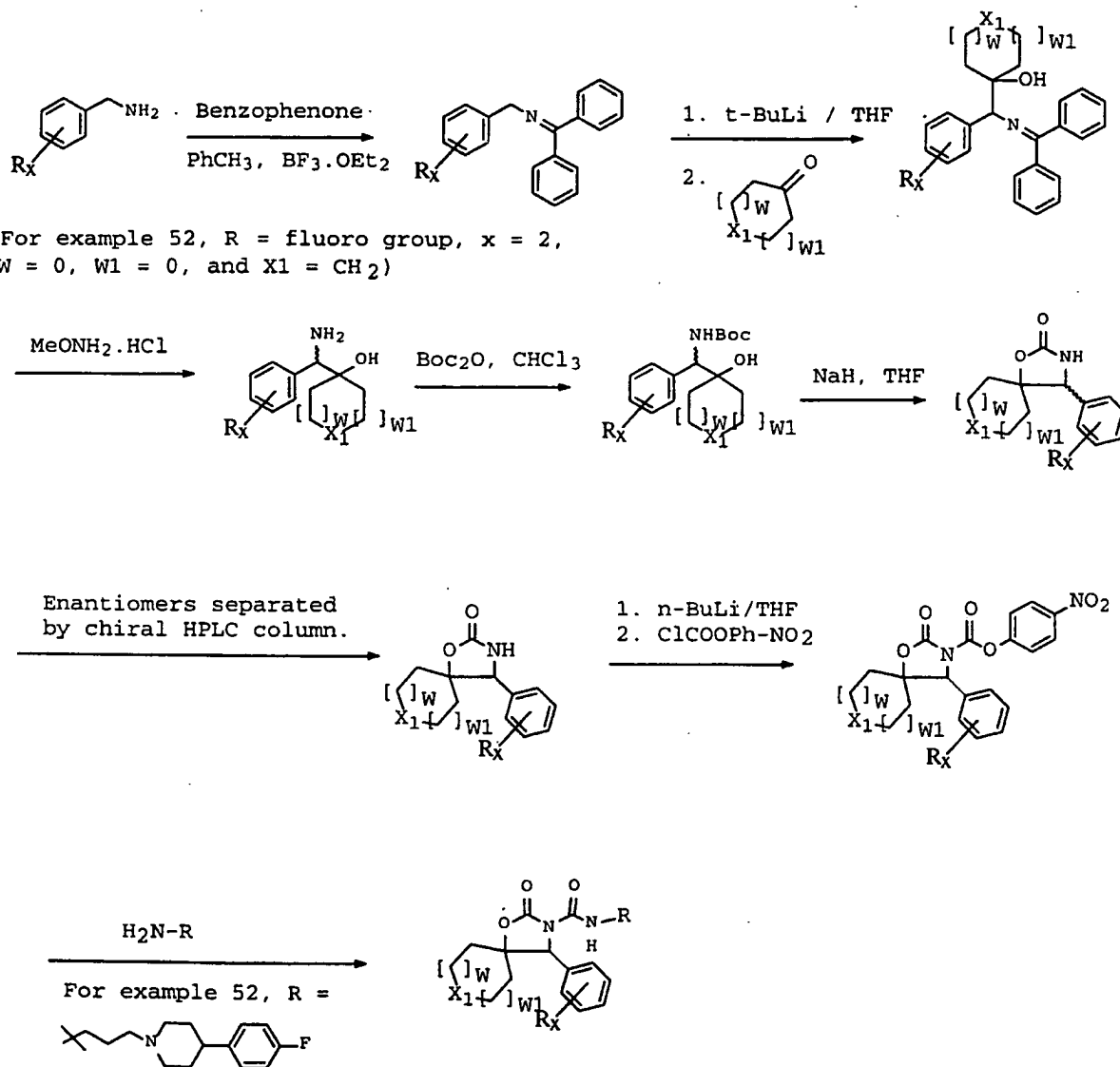


Scheme 27 Preparation of Examples 46 and 47.



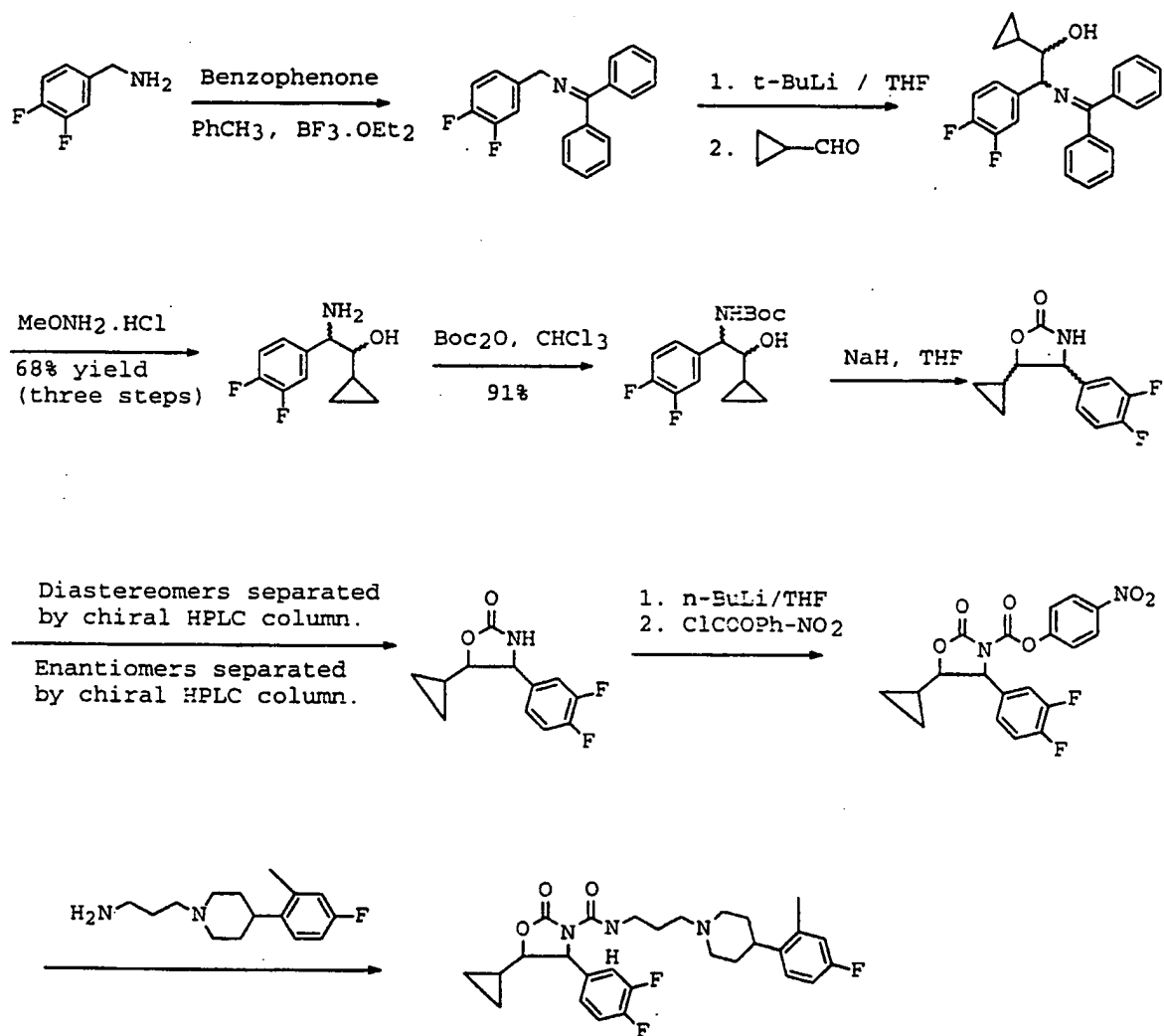
Scheme 28: Preparation of Example 50.

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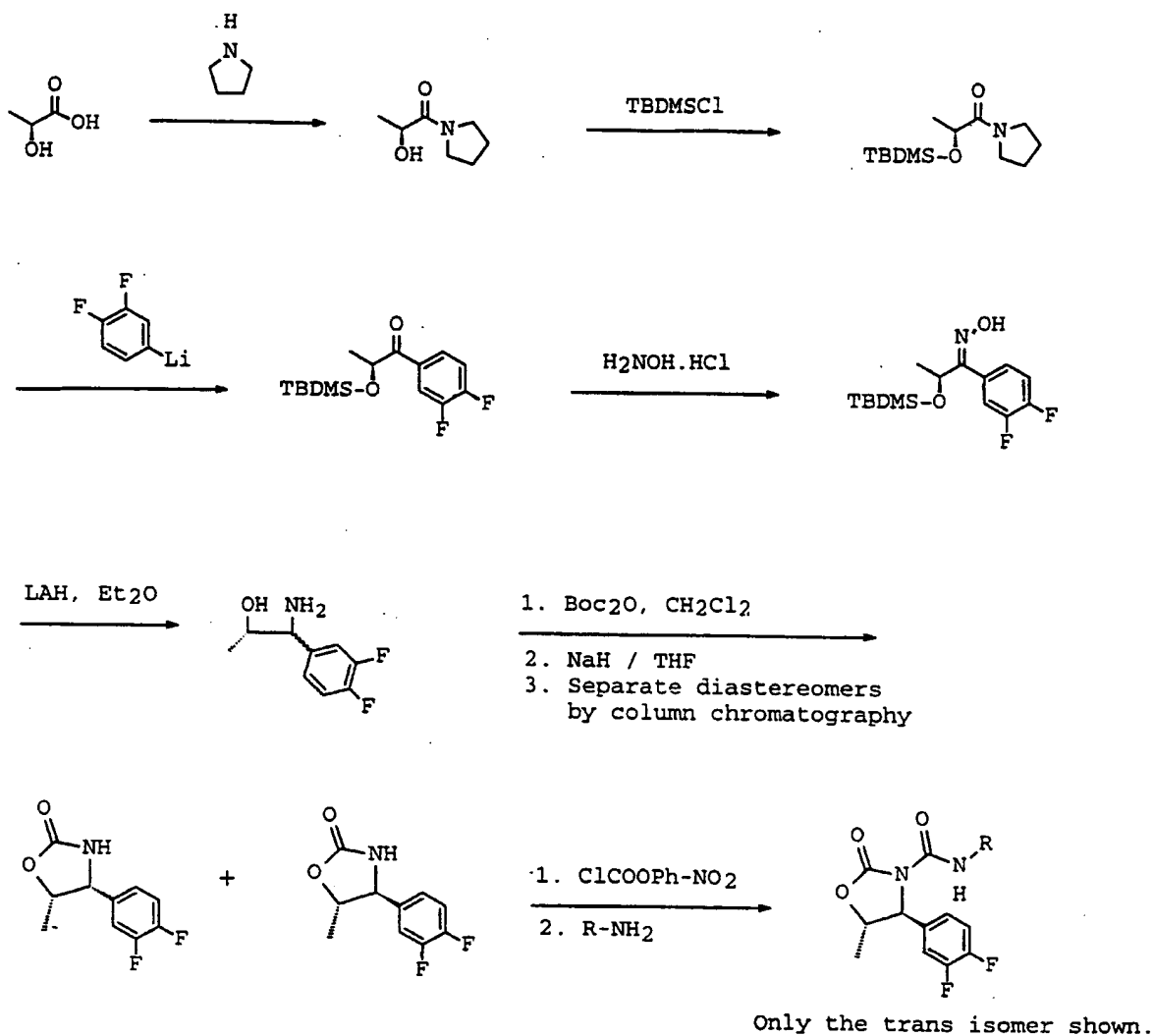
Scheme 29: Synthesis of Example 52 and related compounds

-197-



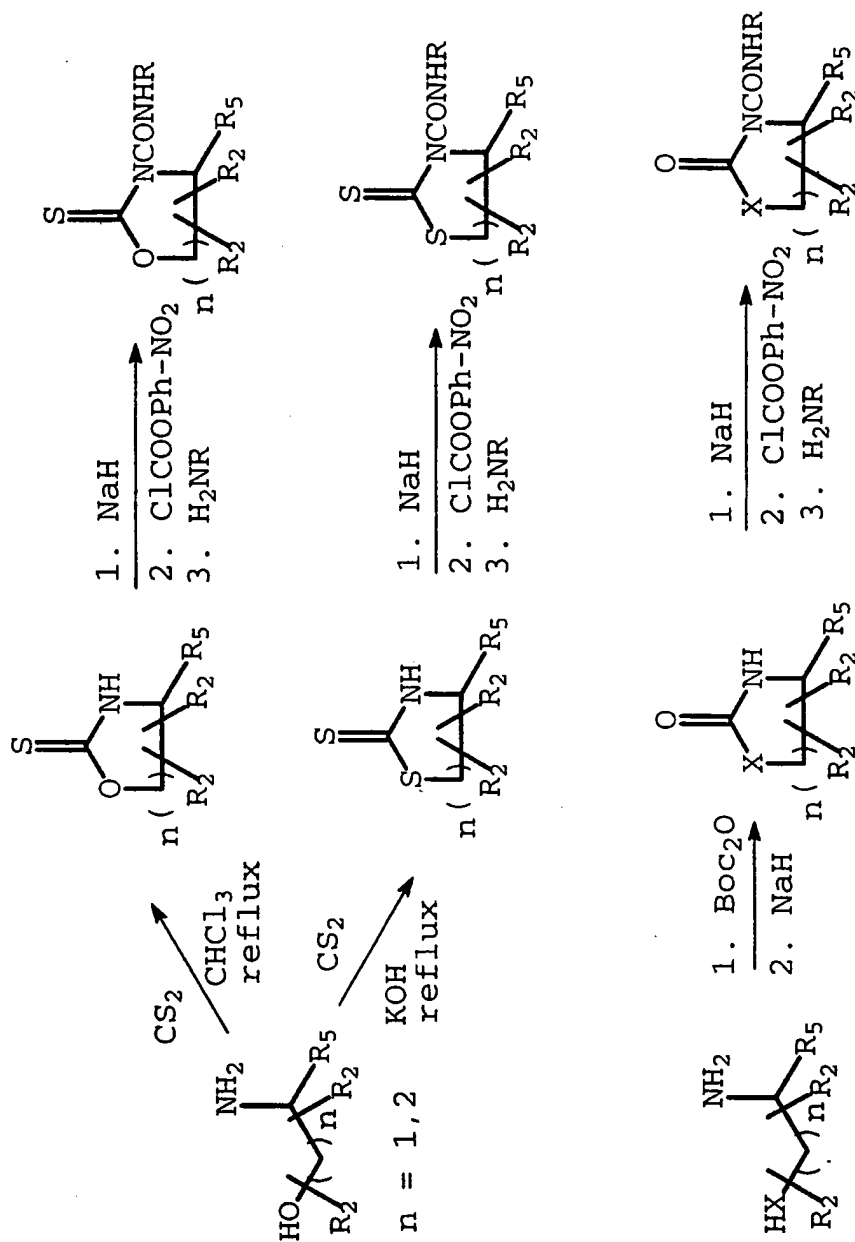
Scheme 30: Synthesis of Example 53.

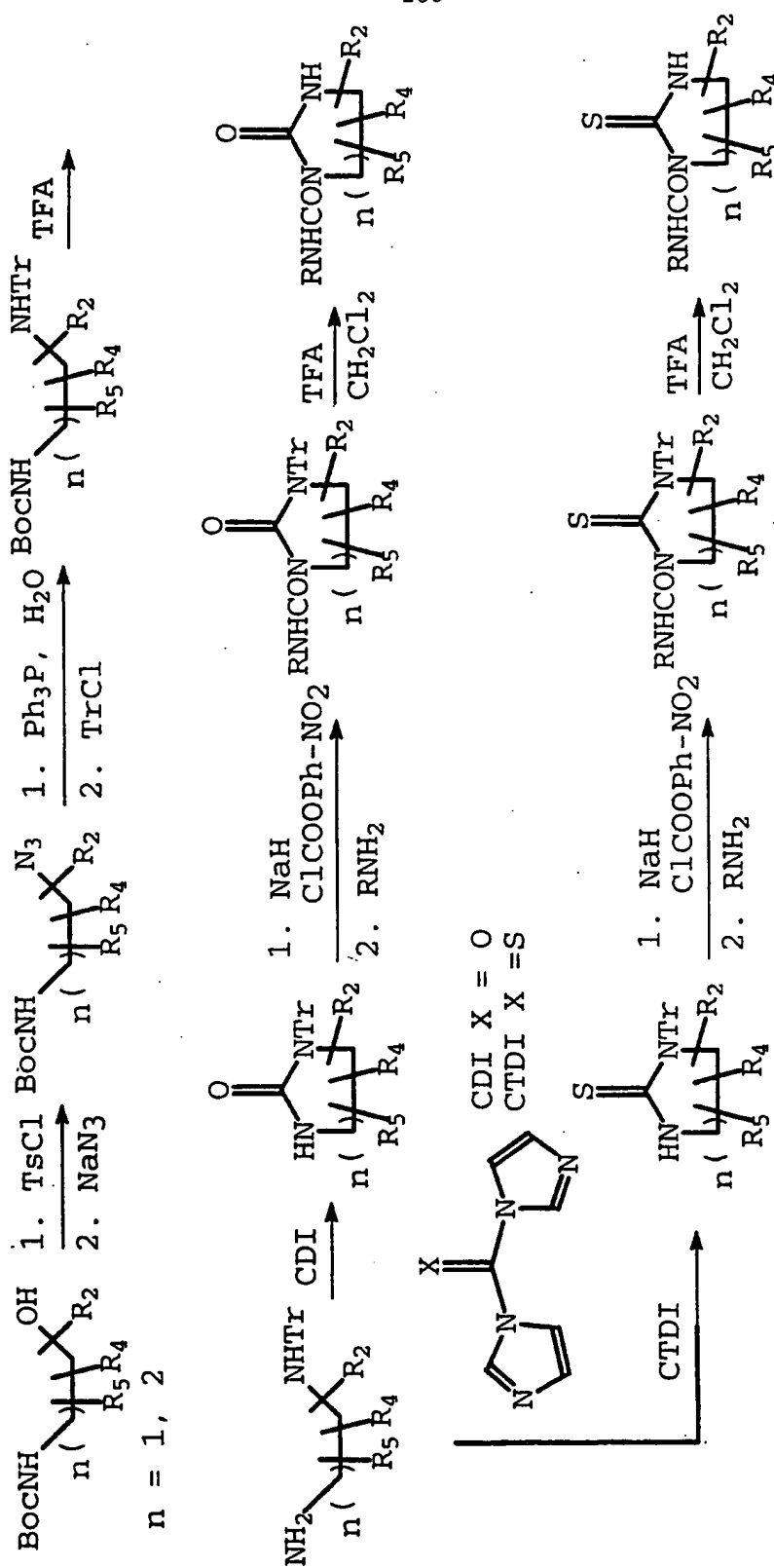
-198-



Scheme 31: General synthesis of methylated oxazolidinone.

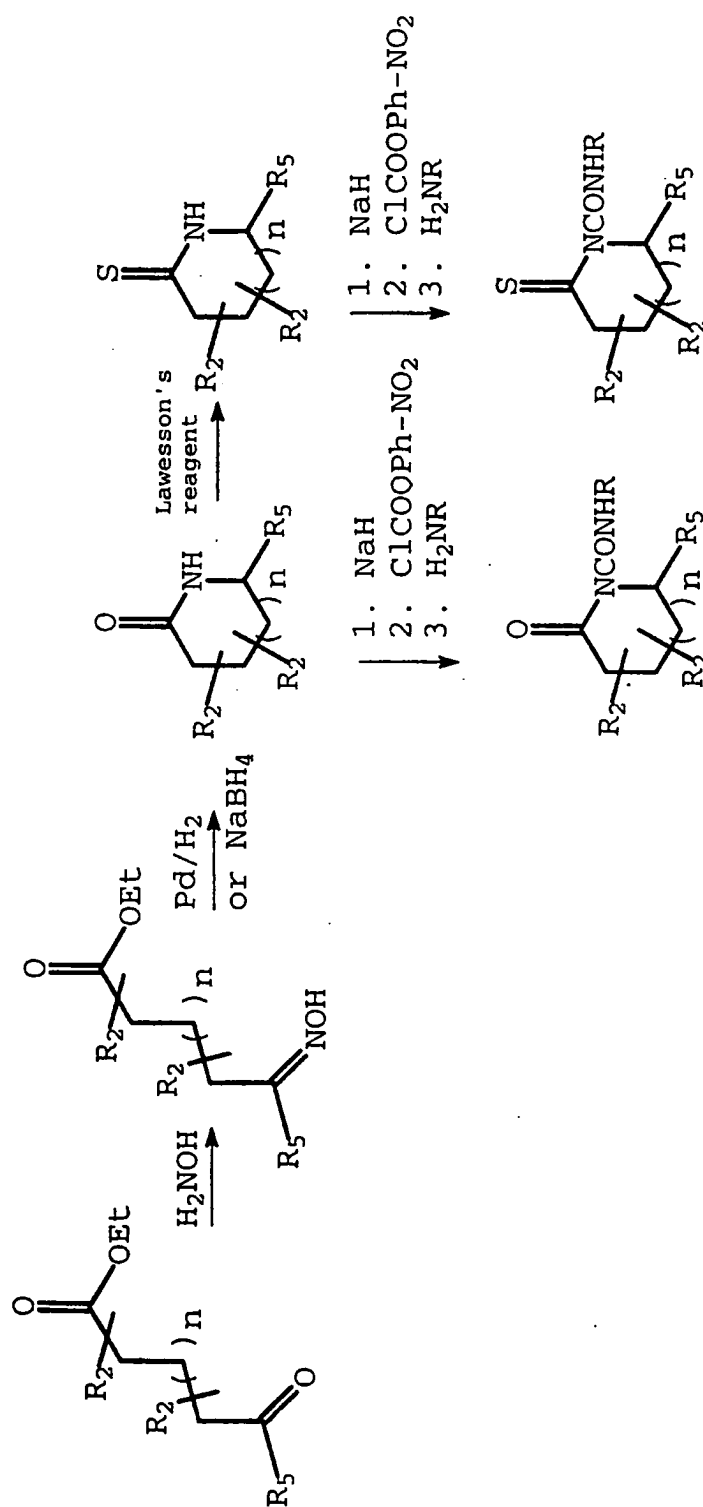
-199-

**Scheme 32:** General synthetic scheme.

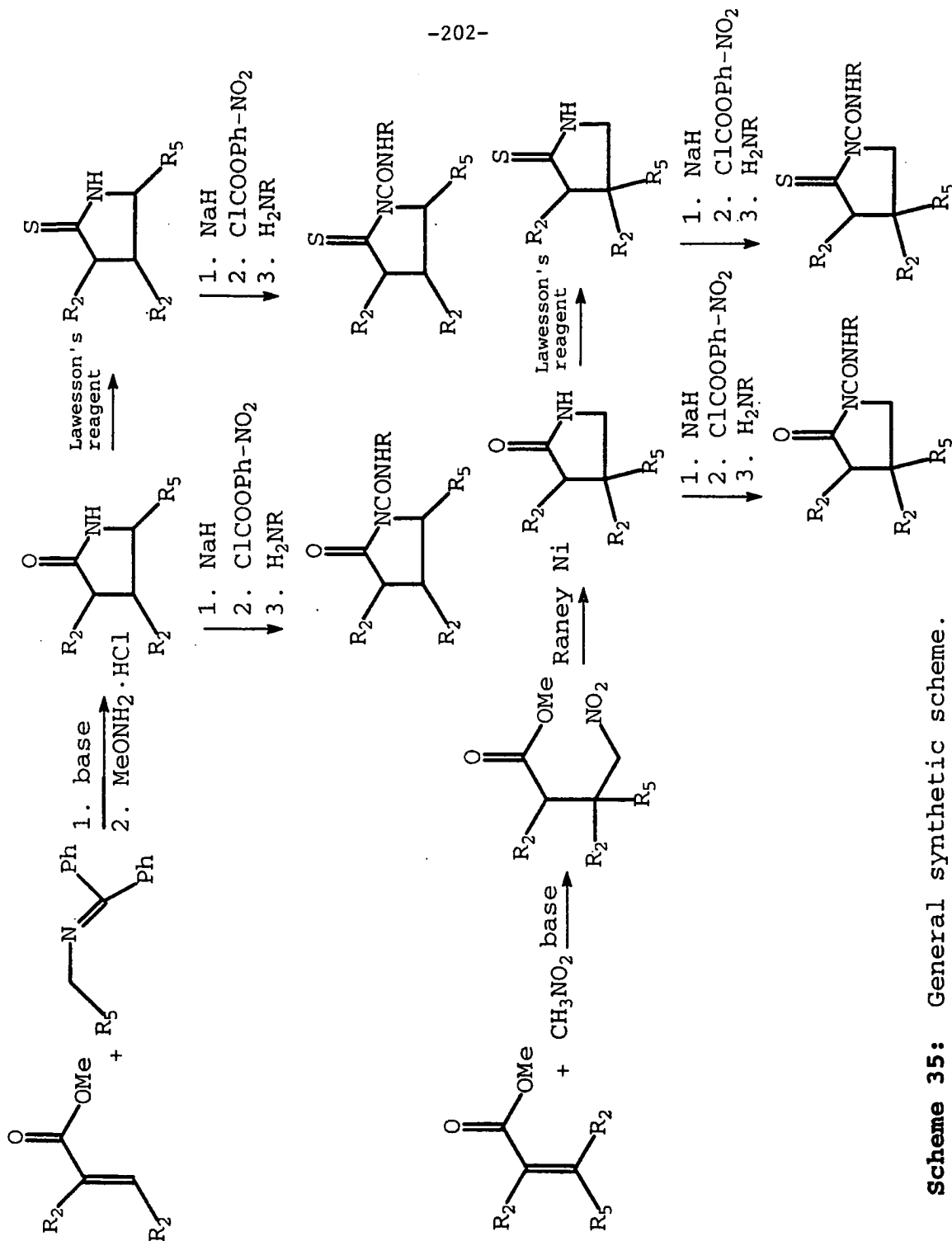


Scheme 33: General synthetic scheme.

-201-

**Scheme 34:** General synthetic scheme.

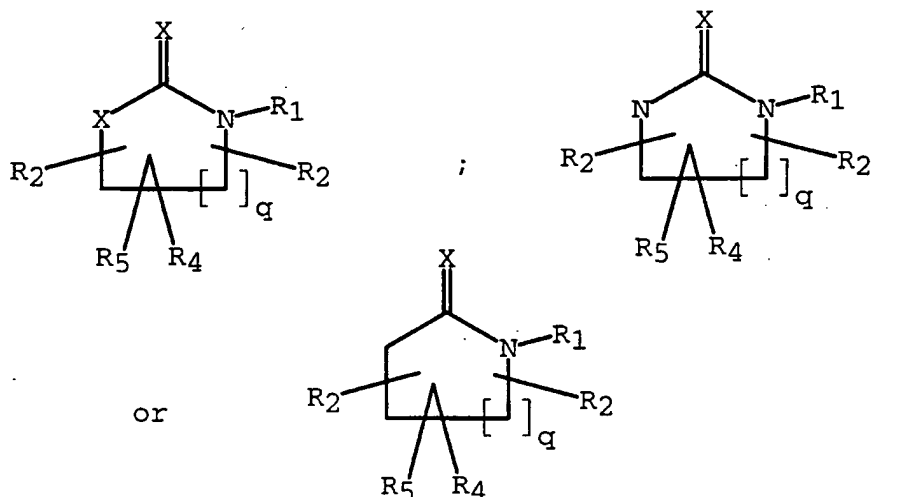
-202-

**Scheme 35:** General synthetic scheme.

-203-

What is claimed is:

1. A compound having the structure:



5 wherein each X is independently O or S;

wherein q is 1 or 2;

10 wherein each R₂ is independently H; -(CH₂)_tXR₃; -
 (CH₂)_tC(X)NR₃; -(CH₂)_tCO₂R₃; -CO₂R₃; straight chained
 or branched C₁-C₇ alkyl, aminoalkyl,
 carboxamidoalkyl; straight chained or branched C₂-
 C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇
 cycloalkenyl;

15 wherein each t is an integer from 1 to 4 inclusive;

20 wherein each R₃ is independently H; straight
 chained or branched C₁-C₇ alkyl, straight chained
 or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇

cycloalkyl or C₅-C₇ cycloalkenyl;

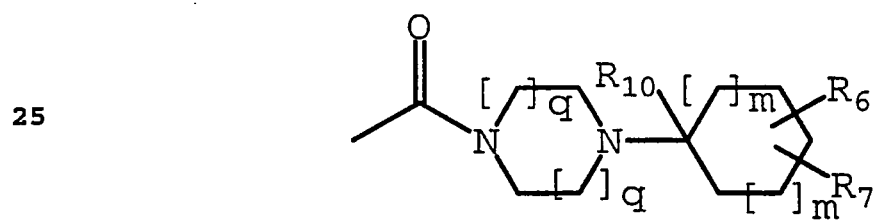
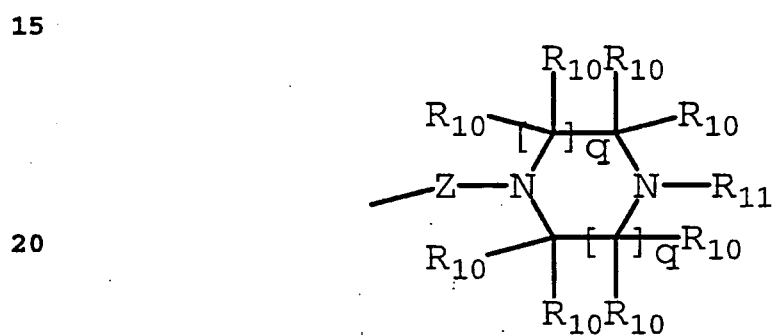
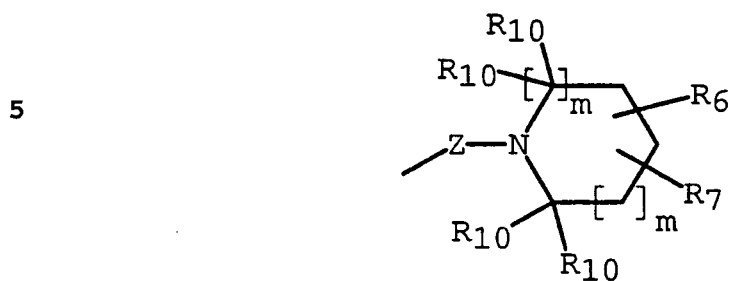
wherein R₄ is aryl, heteroaryl, C₁-C₇ alkyl
substituted with one or two aryl, or C₁-C₇ alkyl
5 substituted with one or two heteroaryl; wherein the
aryl or heteroaryl may be substituted with one or
more of F, Cl, Br, I, -CN, -NO₂, -N(R₃)₂, -COR₃, -
(CH₂)_tXR₃, -(CH₂)_nC(X)NR₃, -(CH₂)_nCO₂R₃, straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl,
10 polyfluoroalkyl or carboxamidoalkyl, or straight
chained or branched C₂-C₇ aminoalkyl, alkenyl or
alkynyl, or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

wherein each n independently is an integer from 0
15 to 7 inclusive;

wherein R₅ is H; aryl, C₁-C₇ alkyl substituted with
aryl, heteroaryl, or C₁-C₇ alkyl substituted with
heteroaryl; wherein the aryl or heteroaryl may be
20 substituted with one or more of F, Cl, Br, I, -CN,
-NO₂, -N(R₃)₂, -COR₃, -(CH₂)_tXR₃, -(CH₂)_nC(X)NR₃, -
(CH₂)_nCO₂R₃, straight chained or branched C₁-C₇
alkyl, monofluoroalkyl, polyfluoroalkyl or
carboxamidoalkyl, or straight chained or branched
25 C₂-C₇ aminoalkyl, alkenyl or alkynyl, or C₃-C₇
cycloalkyl or C₅-C₇ cycloalkenyl;

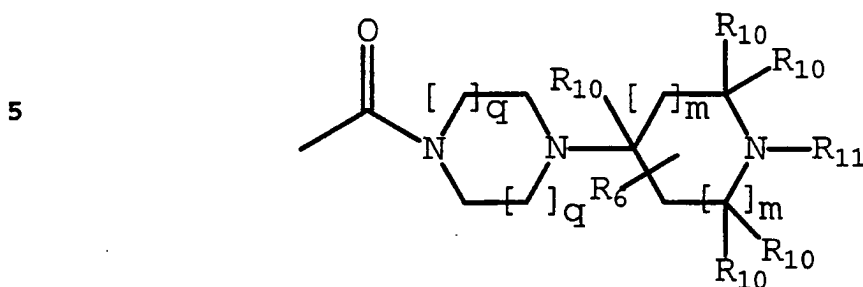
where R₅ and one R₂ on adjacent carbon atoms
together may form aryl, heteroaryl, indane or
30 tetrahydronaphthyl, C₃-C₇ cycloalkyl, or
heterocycloalkyl wherein one or two heteroatoms may
be O, N or S;

wherein R_1 is



or

35



where each R_6 is independently H; straight chained or branched C_1 - C_7 alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 - C_7 cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -
 15
 20
 25
 30
 35

where each R_7 is independently H; F; Cl; Br; I; -
 COR_3 ; $-CO_2R_3$; $-(CH_2)_nXR_3$; $(CH_2)_nC(X)N(R_3)_2$; -
 $(CH_2)_nCO_2R_3$; $-CN$; $-NO_2$; $-N(R_3)_2$; straight chained or
 branched C_1 - C_7 alkyl, hydroxyalkyl, aminoalkyl,
 carboxamidoalkyl, alkoxyalkyl, monofluoroalkyl or
 polyfluoroalkyl; straight chained or branched C_2 - C_7
 alkenyl or alkynyl; C_3 - C_7 cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or C_5 - C_7
 cycloalkenyl, wherein the alkyl, aminoalkyl,

carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 - C_7 cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1 - C_7 alkyl, straight chained or branched C_1 - C_7 monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 - C_7 cycloalkenyl;

wherein each R_{10} is independently H; $(CH_2)_tXR_3$; $(CH_2)_tC(X)NR_3$; $(CH_2)_tCO_2R_3$; straight chained or branched C_1 - C_7 alkyl or carboxamidoalkyl; straight chained or branched C_2 - C_7 aminoalkyl, alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

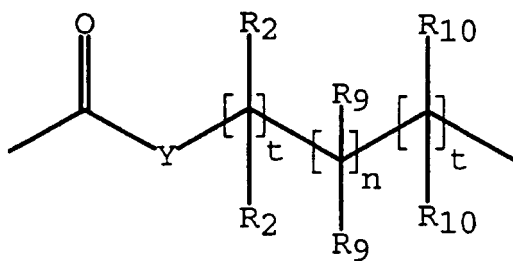
wherein R_{11} is aryl, heteroaryl, C_1 - C_7 alkyl substituted with one or two aryl, or C_1 - C_7 alkyl substituted with one or two heteroaryl; wherein any aryl or heteroaryl independently may be substituted with one or more of F, Cl, Br, I, $-CN$, $-NO_2$, $-N(R_3)_2$, $-COR_3$, $-(CH_2)_nXR_3$, $-(CH_2)_nC(X)NR_3$, $-(CH_2)_nCO_2R_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, or

carboxamidoalkyl, straight chained or branched C₂-C₇, aminoalkyl, alkenyl, or alkynyl, or C₃-C₇, cycloalkyl or C₅-C₇, cycloalkenyl;

5 wherein each m independently is an integer from 0 to 3 inclusive;

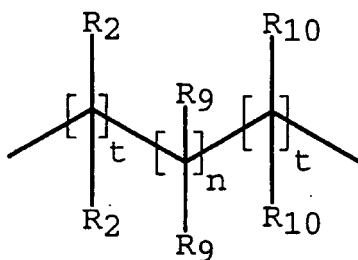
wherein Z is

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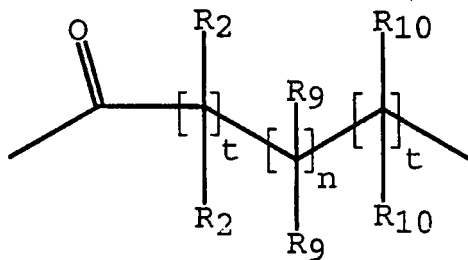
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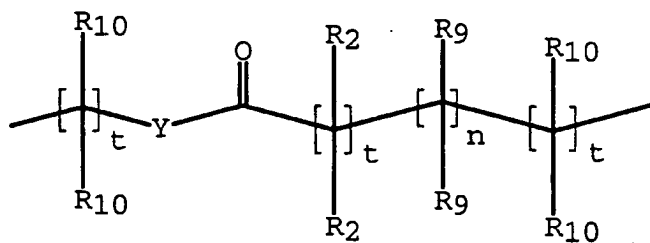
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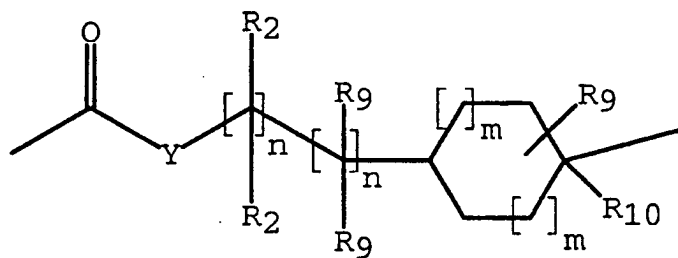
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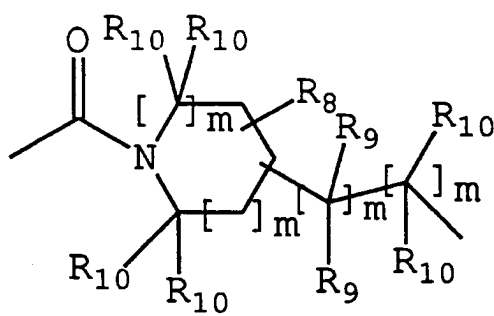
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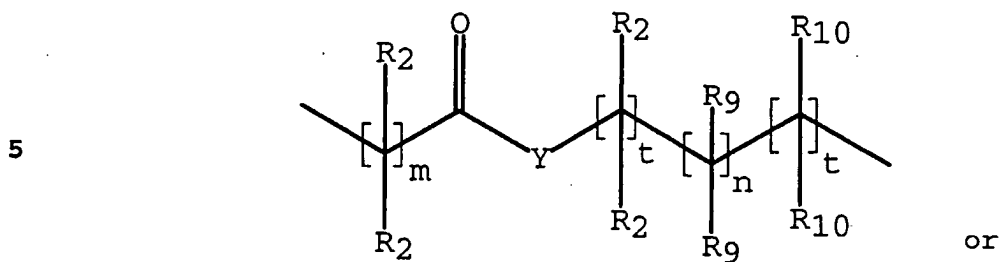


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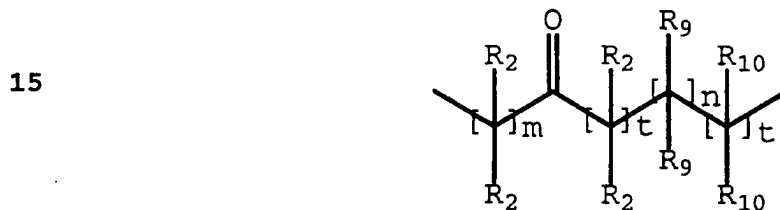
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10



20

or C₂-C₇ alkenyl, wherein the C₂-C₇ alkenyl may be unsubstituted or substituted with one or more R₉ groups;

25

where R₈ is H; (CH₂)_tXR₃; (CH₂)_tC(X)NR₃; (CH₂)_tCO₂R₃; straight chained or branched C₁-C₇ alkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ aminoalkyl, alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

30

where each R₉ is independently H; F; Cl; Br; I; (CH₂)_mXR₃; (CH₂)_mC(X)NR₃; (CH₂)_mCO₂R₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;

35

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straight chained or branched C_2-C_7 alkenyl, or
alkynyl; or C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl;

wherein Y is S, O, or NR_8 ;

5

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound
comprises the (+) enantiomer.

10

3. The compound of claim 1, wherein the compound
comprises the (-) enantiomer.

4. The compound of claim 1, wherein the compound
comprises a *cis* isomer.

15

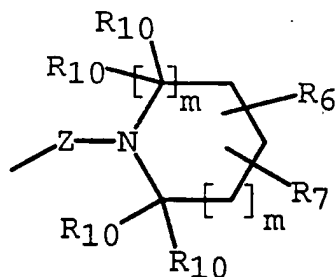
5. The compound of claim 1, wherein the compound
comprises a *trans* isomer.

6. The compound of claim 1, wherein

20

R_1 is

25



30

R_4 is aryl or heteroaryl, wherein the aryl may be
substituted with one or more of F, Cl, $-(CH_2)_cOR_3$, $-(CH_2)_nC(O)NR_3$, $-(CH_2)_nCO_2R_3$, straight chained or

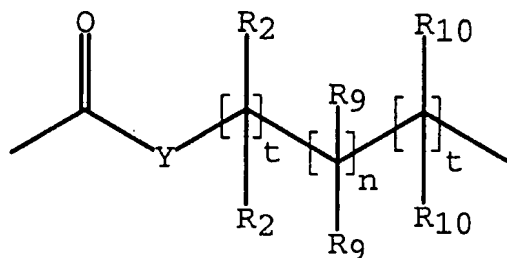
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branched C₁-C₇ alkyl or monofluoroalkyl; and

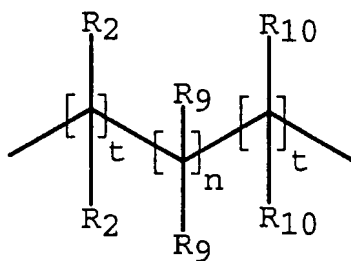
Z is

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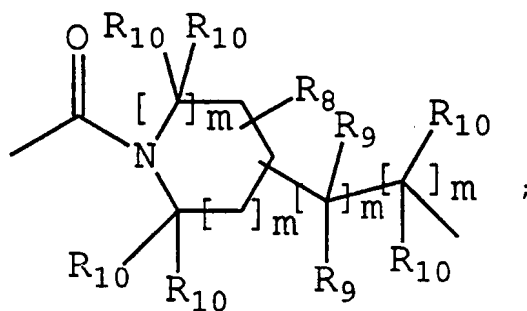


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or

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30



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7. The compound of claim 6, wherein R₄ is pyridyl or

phenyl, wherein the phenyl may be substituted with one or more of F, Cl, $-(CH_2)_tOR_3$, $-(CH_2)_nC(O)NR_3$, $-(CH_2)_nCO_2R_3$, straight chained or branched C_1 - C_7 alkyl or monofluoroalkyl.

5

8. The compound of claim 7, wherein each R_6 is independently aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl.

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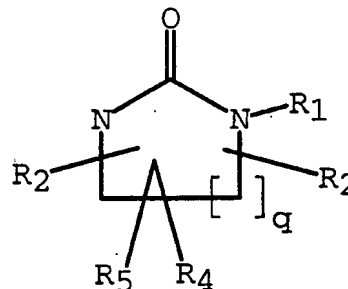
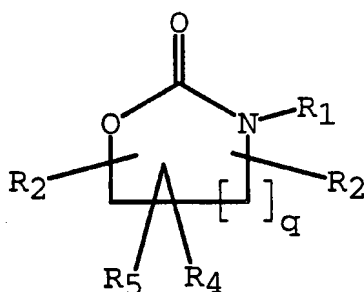
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9. The compound of claim 8, wherein R_7 is H; $-CN$; $-CO_2R_3$; $-C(O)NR_3$; $-(CH_2)_mXR_3$; unsubstituted or substituted aryl; C_1 - C_3 alkyl; or $-OCOR_3$.

20

10. The compound of claim 9, wherein the R_4 is phenyl, wherein the phenyl may be substituted with at least one of F or Cl.

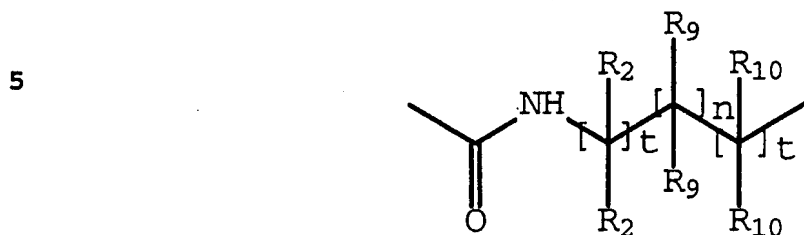
11. The compound of claim 10 having the structure:



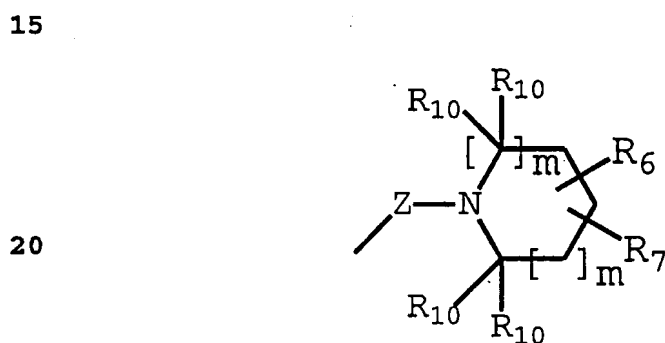
or

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12. The compound of claim 11, wherein Z is:



13. The compound of claim 12, wherein q is 1 and R₁ is



25 14. The compound of claim 13, wherein at least one R₂ is C₁-C₃ alkyl.

30 15. The compound of claim 13, wherein R₄ is phenyl substituted with at least one of F or Cl.

16. The compound of claim 15, wherein R₄ is phenyl substituted with at least two F.

35 17. The compound of claim 12, wherein R₄ is 3,4-

difluorophenyl.

18. The compound of claim 13, wherein R_6 is pyridyl, phenyl, or phenyl substituted with one or more of
5 F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl.
19. The compound of claim 13, wherein R_7 is H; $-CN$; or
10 $-CO_2R_3$.
20. The compound of claim 13, wherein R_9 is F; $-OH$; C_1 - C_3 alkyl; or $-(CH_2)_mXR_3$.
15
21. The compound of claim 18, wherein R_6 is 4-fluorophenyl.
22. A pharmaceutical composition comprising a
20 therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.
23. The pharmaceutical composition of claim 22 wherein
25 the amount of the compound is an amount from about 0.01 mg to about 800 mg.
24. The pharmaceutical composition of claim 23 wherein
30 the amount of the compound is an amount from about 0.01 mg to about 500 mg.
25. The pharmaceutical composition of claim 24 wherein
the amount of the compound is an amount from about 0.01 mg to about 250 mg.
26. The pharmaceutical composition of claim 25 wherein
35

the amount of the compound is from about 0.1 mg to about 60 mg.

5 27. The pharmaceutical composition of claim 26 wherein the amount of the compound is from about 1 mg to about 20 mg.

10 28. The pharmaceutical composition of claim 22, wherein the carrier is a liquid and the composition is a solution.

15 29. The pharmaceutical composition of claim 22, wherein the carrier is a solid and the composition is a tablet.

20 30. The pharmaceutical composition of claim 22, wherein the carrier is a gel and the composition is a suppository.

25 31. The pharmaceutical composition of claim 22, wherein the compound additionally does not cause a fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.

30 32. A method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim 1 effective to treat benign prostatic hyperplasia.

35 33. A method of claim 32, wherein the compound additionally does not cause a fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.

34. The method of claim 33, wherein the compound effects treatment of benign prostatic hyperplasia by relaxing lower urinary tract tissue.
- 5 35. The method of claim 34, wherein lower urinary tract tissue is prostatic smooth muscle.
- 10 36. A method of treating a subject suffering from high intraocular pressure which comprises administering to the subject an amount of the compound of claim 1 effective to lower intraocular pressure.
- 15 37. A method of treating a subject suffering from a disorder associated with high cholesterol which comprises administering to the subject an amount of the compound of claim 1 effective to inhibit cholesterol synthesis.
- 20 38. A method of treating a disease which is susceptible to treatment by antagonism of the α_{1A} receptor which comprises administering to the subject an amount of the compound of claim 1 effective to treat the disease.
- 25 39. A method of treating a subject suffering from impotency which comprises administering to the subject an amount of the compound of claim 1 effective to treat impotency.
- 30 40. A method of treating a subject suffering from sympathetically mediated pain which comprises administering to the subject an amount of the compound of claim 1 effective to treat sympathetically mediated pain.

41. A method of treating a subject suffering from cardiac arrhythmia which comprises administering to the subject an amount of the compound of claim 1 effective to treat cardiac arrhythmia.
- 5
42. A method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim 1 effective to treat benign
- 10
- prostatic hyperplasia.
43. The method of claim 42, wherein the compound effects treatment of benign prostatic hyperplasia by relaxing lower urinary tract tissue.
- 15
44. The method of claim 43, wherein lower urinary tract tissue is prostatic smooth muscle.
45. A method of treating a subject suffering from
- 20
- benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim 1 in combination with a 5 alpha-reductase inhibitor effective to treat benign
- 25
- prostatic hyperplasia.
46. The method of claim 45, wherein the 5-alpha reductase inhibitor is finasteride.
47. A method of treating a subject suffering from
- 30
- benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim 1 in combination with a 5 alpha-reductase inhibitor effective to treat benign
- 35
- prostatic hyperplasia.

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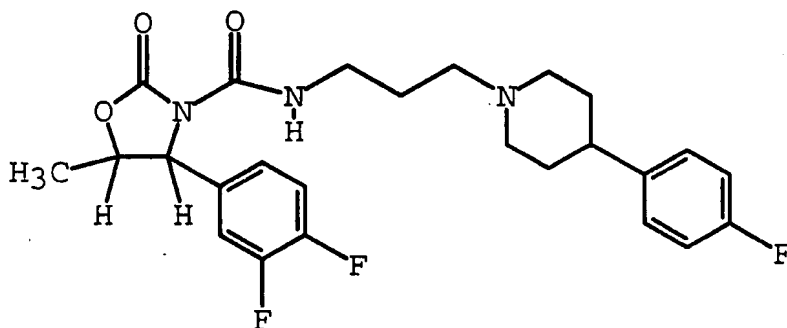
48. The method of claim 47, wherein the 5-alpha reductase inhibitor is finasteride.
- 5 49. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 in combination with a therapeutically effective amount of finasteride and a pharmaceutically acceptable carrier.
- 10 50. The pharmaceutical composition of claim 49 wherein the compound is present in an amount from about 0.01 mg to about 500 mg and the therapeutically effective amount of the finasteride is about 5 mg.
- 15 51. The pharmaceutical composition of claim 50 wherein the compound is present in an amount from about 0.1 mg to about 60 mg and the therapeutically effective amount of finasteride is about 5 mg.
- 20 52. The pharmaceutical composition of claim 51 wherein the compound is present in an amount from about 1 mg to about 20 mg and the therapeutically effective amount of finasteride is about 5 mg.
- 25 53. A method of relaxing lower urinary tract tissue which comprises contacting the lower urinary tract tissue with an amount of the compound of claim 1 effective to relax lower urinary tract tissue.
- 30 54. The method of claim 53, wherein the lower urinary tract tissue is prostatic smooth muscle.
- 35 55. A method of relaxing lower urinary tract tissue in a subject which comprises administering to the subject an amount of the compound of claim 1

effective to relax lower urinary tract tissue.

56. The method of claim 55, wherein the lower urinary tract tissue is prostatic smooth muscle.

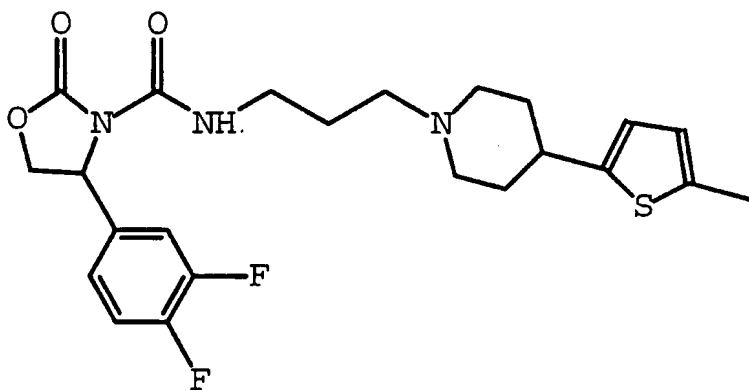
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57. A *trans* (+) isomer of the compound of claim 21, wherein the compound has the structure:



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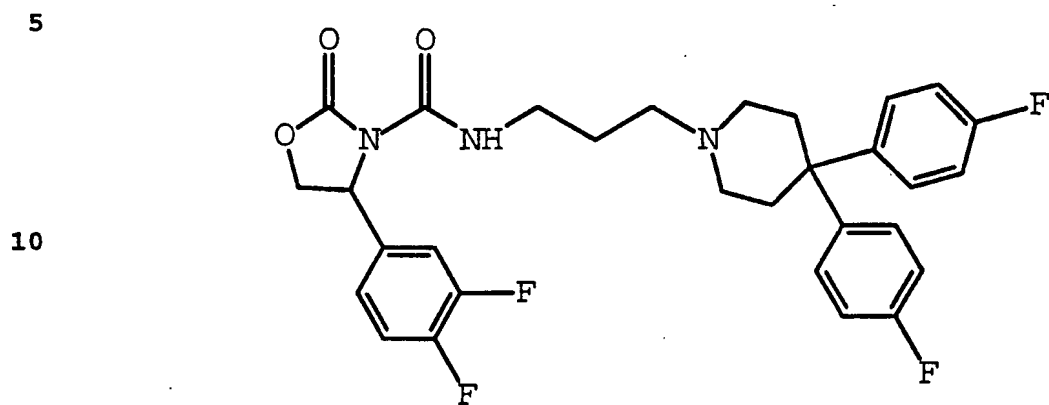
58. The compound of claim 1, wherein the compound has the structure:



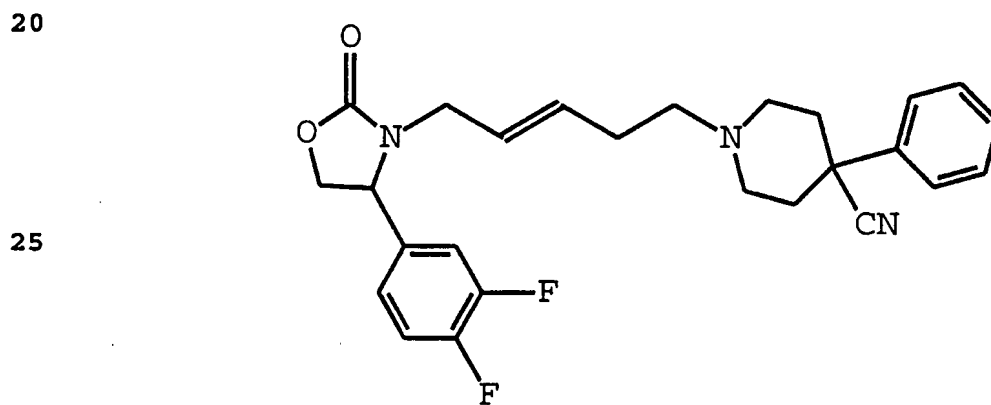
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59. The compound of claim 1, wherein the compound has the structure:



60. The compound of claim 1, wherein the compound has the structure:

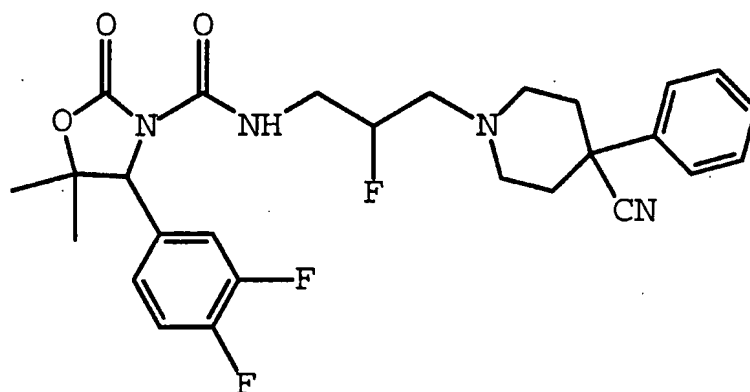


61. The compound of claim 1, wherein the compound has the structure:

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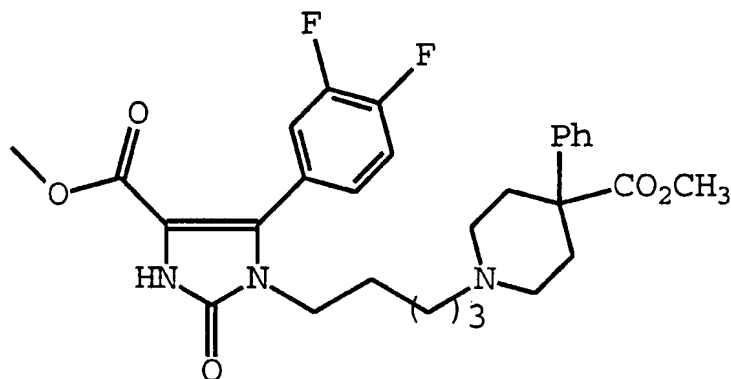
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62. A compound having the structure:

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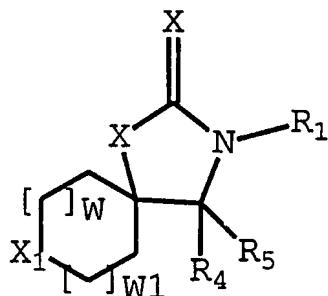


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63. A compound having the structure:

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wherein each W is an integer from 0 to 3 inclusive;

wherein each W1 is an integer from 0 to 3 inclusive;

5

wherein each X is independently O or S;

wherein X1 is O, S, NR₃;

10

wherein each R₂ is independently H; -(CH₂)_tXR₃; -(CH₂)_tC(X)NR₃; -(CH₂)_tCO₂R₃; -CO₂R₃; straight chained or branched C₁-C₇ alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

15

wherein each t is an integer from 1 to 4 inclusive;

20

wherein each R₃ is independently H; straight chained or branched C₁-C₇ alkyl, straight chained or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

25

wherein R₄ is aryl, heteroaryl, C₁-C₇ alkyl substituted with one or two aryl, or C₁-C₇ alkyl substituted with one or two heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -N(R₃)₂, -COR₃, -(CH₂)_tXR₃, -(CH₂)_nC(X)NR₃, -(CH₂)_nCO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or straight chained or branched C₂-C₇ aminoalkyl, alkenyl or alkynyl, or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

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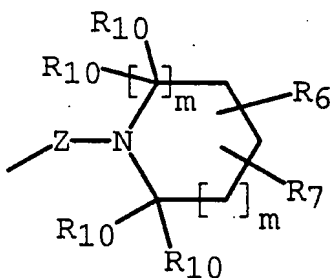
wherein each n independently is an integer from 0

-224-

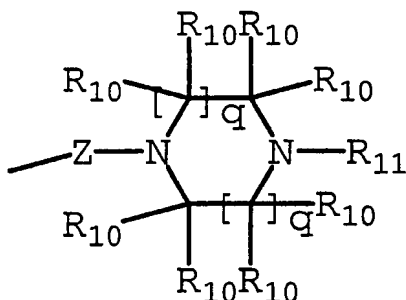
to 7 inclusive;

wherein R_5 is H; aryl, C_1 - C_7 alkyl substituted with
 aryl, heteroaryl, or C_1 - C_7 alkyl substituted with
 heteroaryl; wherein the aryl or heteroaryl may be
 substituted with one or more of F, Cl, Br, I, -CN,
 -NO₂, -N(R₃)₂, -COR₃, -(CH₂)_tXR₃, -(CH₂)_nC(X)NR₃, -
 (CH₂)_nCO₂R₃, straight chained or branched C_1 - C_7
 alkyl, monofluoroalkyl, polyfluoroalkyl or
 carboxamidoalkyl, or straight chained or branched
 C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7
 cycloalkyl or C_5 - C_7 cycloalkenyl;

wherein R_1 is

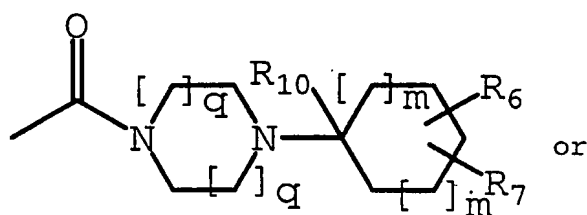


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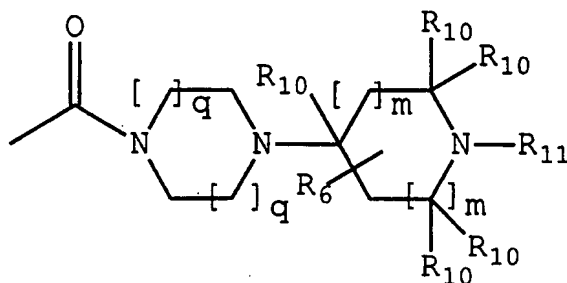


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where each R_6 is independently H; straight chained or branched C_1 - C_7 alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 - C_7 cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -
 $(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$,

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5 -NO₂, -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl;

where each R₃ is independently H; F; Cl; Br; I; -COR₃; -CO₂R₃; -(CH₂)_nXR₃; (CH₂)_nC(X)N(R₃)₂; - (CH₂)_nCO₂R₃; -CN; -NO₂; -N(R₃)₂; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl, carboxamidoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl, wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -(CH₂)_nXR₃, -COR₃, -(CH₂)_nC(X)N(R₃)₂, -(CH₂)_nCO₂R₃, -CN, -NO₂, -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -(CH₂)_nXR₃, -COR₃, -(CH₂)_nC(X)N(R₃)₂, -(CH₂)_nCO₂R₃, -CN, -NO₂, -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇ cycloalkenyl;

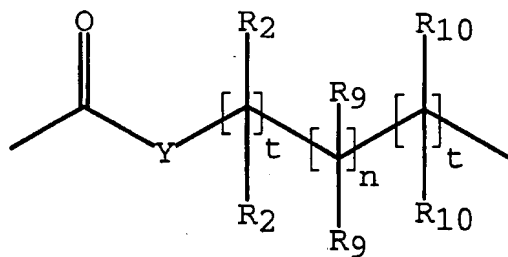
-227-

wherein each R_{10} is independently H; $(CH_2)_tXR_3$;
 $(CH_2)_tC(X)NR_3$; $(CH_2)_tCO_2R_3$; straight chained or
 branched C_1 - C_7 alkyl or carboxamidoalkyl; straight
 chained or branched C_2 - C_7 aminoalkyl, alkenyl, or
 alkynyl; or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

wherein R_{11} is aryl, heteroaryl, C_1 - C_7 alkyl
 substituted with one or two aryl, or C_1 - C_7 alkyl
 substituted with one or two heteroaryl; wherein any
 aryl or heteroaryl independently may be substituted
 with one or more of F, Cl, Br, I, -CN, -NO₂, -
 $N(R_3)_2$, -COR₃, $-(CH_2)_nXR_3$, $-(CH_2)_nC(X)NR_3$, $-(CH_2)_nCO_2R_3$,
 straight chained or branched C_1 - C_7 alkyl,
 monofluoroalkyl, polyfluoroalkyl, or
 carboxamidoalkyl, straight chained or branched C_2 -
 C_7 aminoalkyl, alkenyl, or alkynyl, or C_3 - C_7
 cycloalkyl or C_5 - C_7 cycloalkenyl;

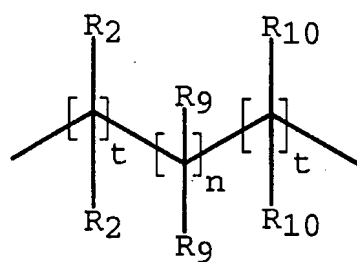
wherein each m independently is an integer from 0
 to 3 inclusive;

wherein Z is



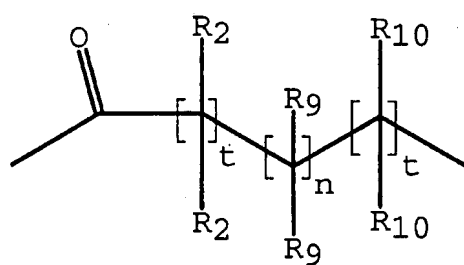
-228-

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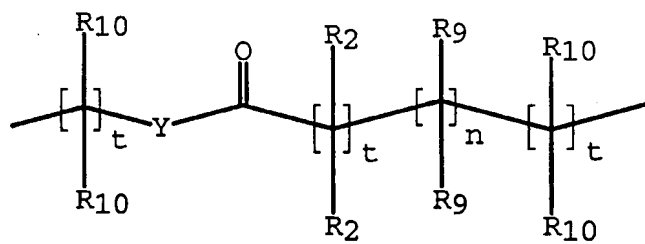
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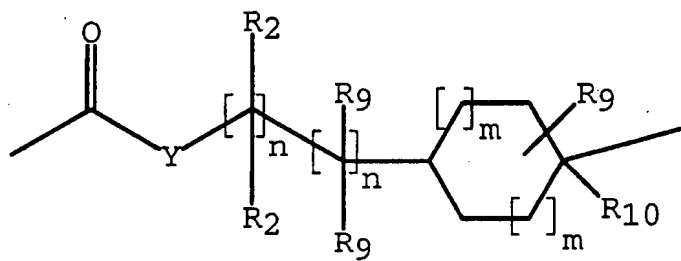
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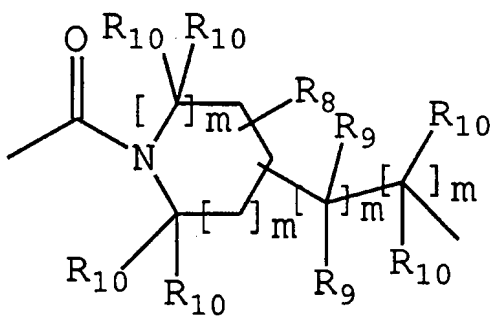
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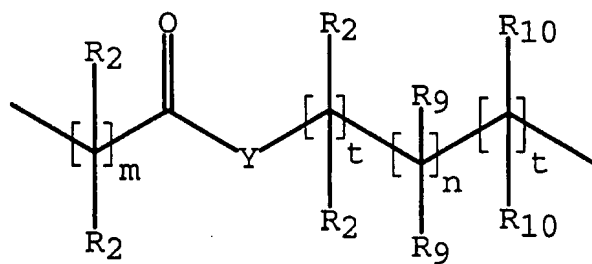
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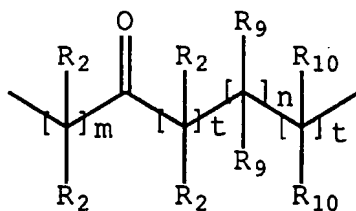
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or

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or C₂-C₇ alkenyl, wherein the C₂-C₇ alkenyl may be unsubstituted or substituted with one or more R₉ groups;

15

where R₈ is H; (CH₂)_tXR₃; (CH₂)_tC(X)NR₃; (CH₂)_tCO₂R₃; straight chained or branched C₁-C₇ alkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ aminoalkyl, alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

20

where each R₉ is independently H; F; Cl; Br; I; (CH₂)_mXR₃; (CH₂)_mC(X)NR₃; (CH₂)_mCO₂R₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

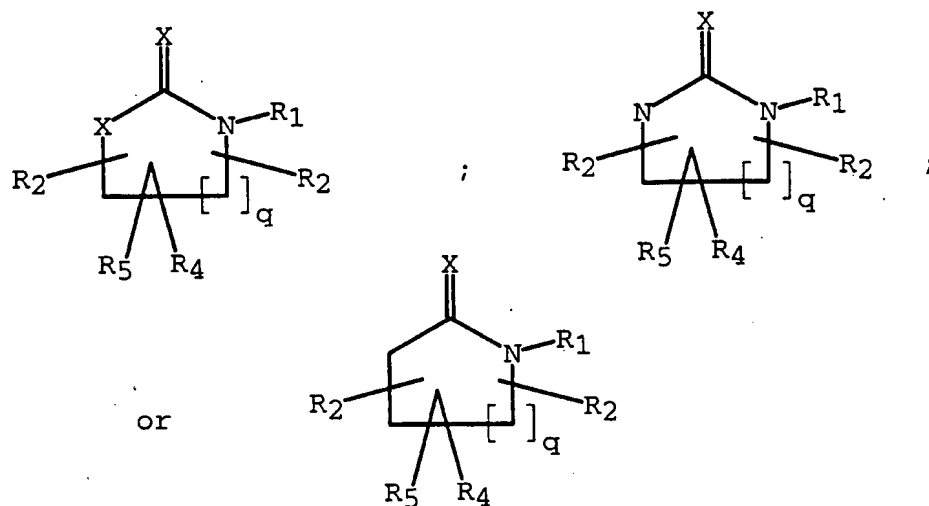
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wherein Y is S, O, or NR₈;

or a pharmaceutically acceptable salt thereof.

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64. A compound having the structure:



5 wherein each X is independently O or S;

wherein q is 1 or 2;

10 wherein each R_2 is independently H; $-(CH_2)_tXR_3$; $-(CH_2)_tC(X)NR_3$; $-(CH_2)_tCO_2R_3$; $-CO_2R_3$; straight chained or branched C_1 - C_7 alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C_2 - C_7 alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

15 wherein each t is an integer from 1 to 4 inclusive;

wherein each R₃ is independently H; straight
chained or branched C₁-C₇ alkyl, straight chained
20 or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇

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cycloalkyl or C₅-C₇ cycloalkenyl;

5 wherein R₄ is aryl, heteroaryl, C₁-C₇ alkyl substituted with one or two aryl, or C₁-C₇ alkyl substituted with one or two heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -N(R₃)₂, -COR₃, -
10 (CH₂)_tXR₃, -(CH₂)_nC(X)NR₃, -(CH₂)_nCO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or straight
15 chained or branched C₂-C₇ aminoalkyl, alkenyl or alkynyl, or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

15 wherein each n independently is an integer from 0 to 7 inclusive;

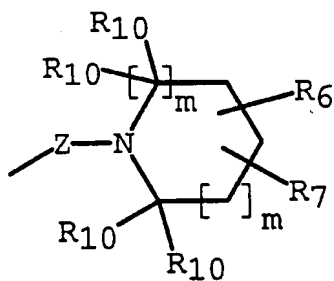
20 wherein R₅ is H; aryl, C₁-C₇ alkyl substituted with aryl, heteroaryl, or C₁-C₇ alkyl substituted with heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -N(R₃)₂, -COR₃, -(CH₂)_tXR₃, -(CH₂)_nC(X)NR₃, -
25 (CH₂)_nCO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or straight chained or branched C₂-C₇ aminoalkyl, alkenyl or alkynyl, or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

30 where R₅ and one R₂ on adjacent carbon atoms together may form aryl, heteroaryl, indane or tetrahydronaphthyl, C₃-C₇ cycloalkyl, or heterocycloalkyl wherein one or two heteroatoms may be O, N or S;

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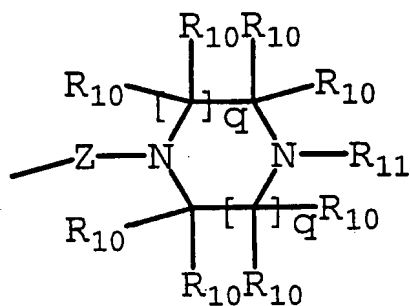
wherein R_1 is

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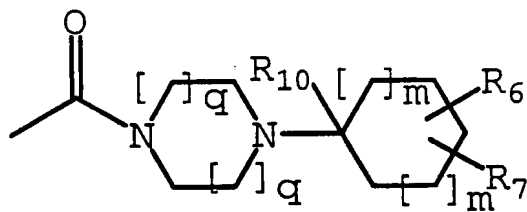
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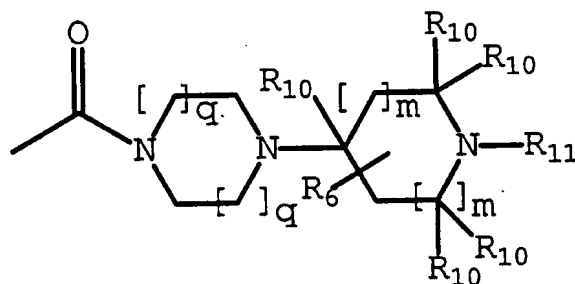
or

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where each R_6 is independently H; straight chained or branched C_1 - C_7 alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 - C_7 cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -
 15 $(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 - C_7 cycloalkenyl;

25

where each R_7 is independently H; F; Cl; Br; I; -
 COR_3 ; $-CO_2R_3$; $-(CH_2)_nXR_3$; $(CH_2)_nC(X)N(R_3)_2$; -
 $(CH_2)_nCO_2R_3$; $-CN$; $-NO_2$; $-N(R_3)_2$; straight chained or
 30 branched C_1 - C_7 alkyl, hydroxyalkyl, aminoalkyl, carboxamidoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5 - C_7 cycloalkenyl, wherein the alkyl, aminoalkyl,

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carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5-C_7 cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5-C_7 cycloalkenyl;

wherein each R_{10} is independently H; $(CH_2)_tXR_3$; $(CH_2)_tC(X)NR_3$; $(CH_2)_tCO_2R_3$; straight chained or branched C_1-C_7 alkyl or carboxamidoalkyl; straight chained or branched C_2-C_7 aminoalkyl, alkenyl, or alkynyl; or C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl;

wherein R_{11} is aryl, heteroaryl, C_1-C_7 alkyl substituted with one or two aryl, or C_1-C_7 alkyl substituted with one or two heteroaryl; wherein any aryl or heteroaryl independently may be substituted with one or more of F, Cl, Br, I, $-CN$, $-NO_2$, $-N(R_3)_2$, $-COR_3$, $-(CH_2)_nXR_3$, $-(CH_2)_nC(X)NR_3$, $-(CH_2)_nCO_2R_3$, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, or

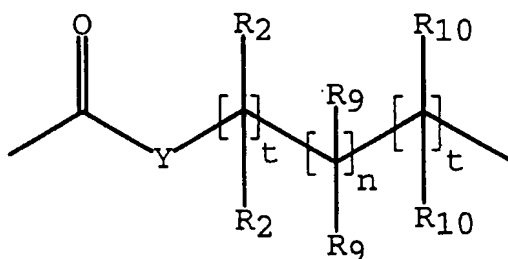
-236-

carboxamidoalkyl, straight chained or branched C₂-C₇, aminoalkyl, alkenyl, or alkynyl, or C₃-C₇, cycloalkyl or C₅-C₇, cycloalkenyl;

5 wherein each m independently is an integer from 0 to 3 inclusive;

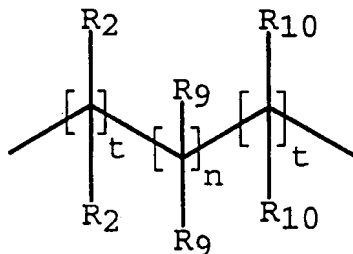
wherein Z is

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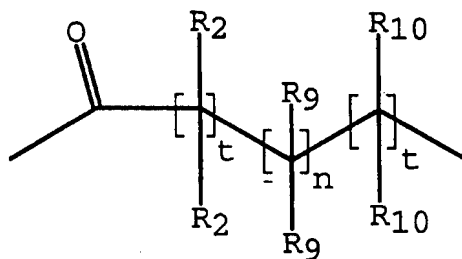
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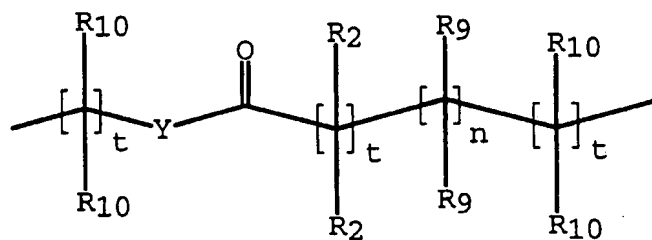


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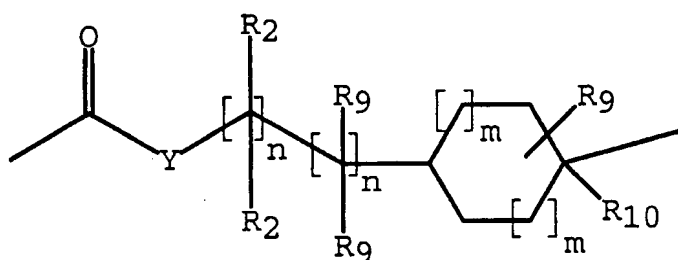
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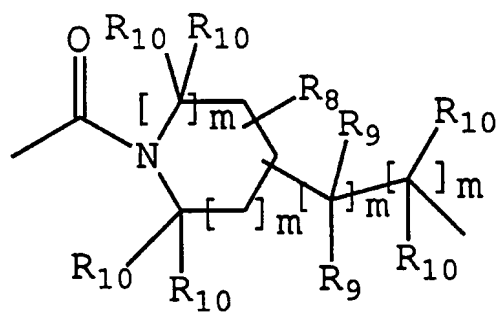
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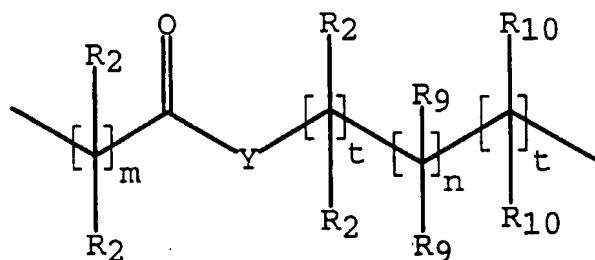


, or

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or C₂-C₇ alkenyl, wherein the C₂-C₇ alkenyl may be unsubstituted or substituted with one or more R₉ groups;

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where R₈ is H; (CH₂)_tXR₃; (CH₂)_tC(X)NR₃; (CH₂)_tCO₂R₃; straight chained or branched C₁-C₇ alkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ aminoalkyl, alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

30

where each R₉ is independently H; F; Cl; Br; I; (CH₂)_mXR₃; (CH₂)_mC(X)NR₃; (CH₂)_mCO₂R₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;

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straight chained or branched C₂-C₇ alkenyl, or
alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

wherein Y is S, O, or NR₈;

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or a pharmaceutically acceptable salt thereof.

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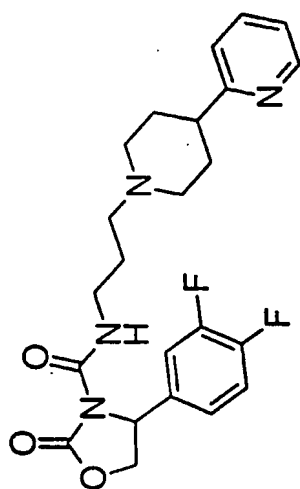
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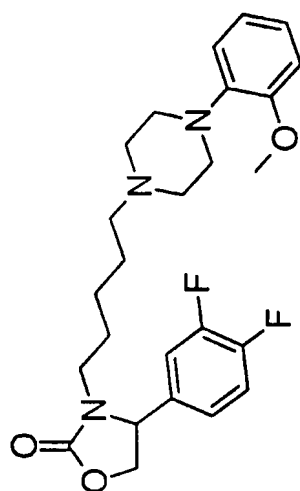
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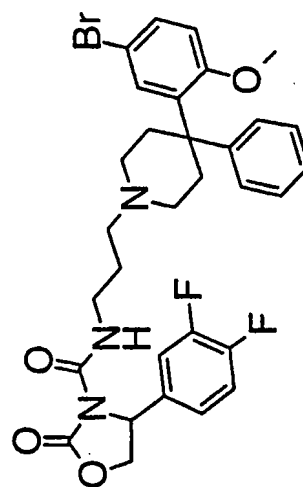
FIG. 1A



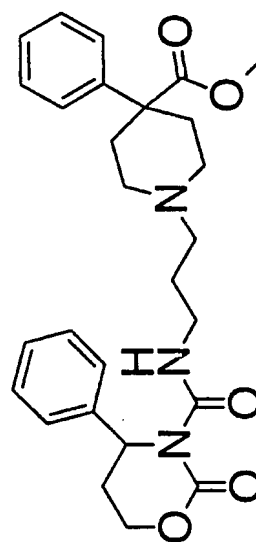
Compound 1



Compound 2

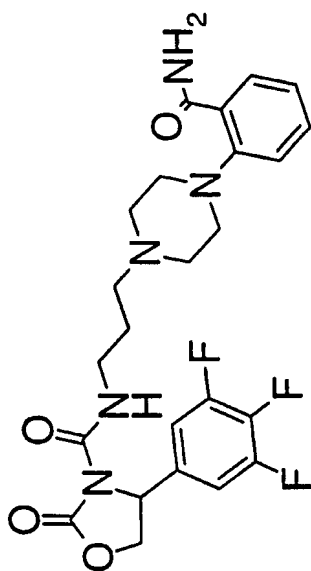


Compound 3

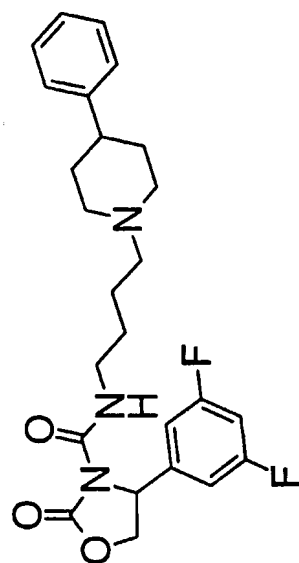


Compound 4

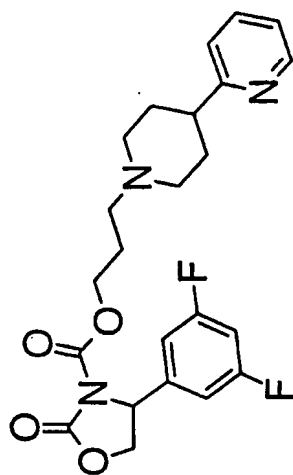
FIG. 1B



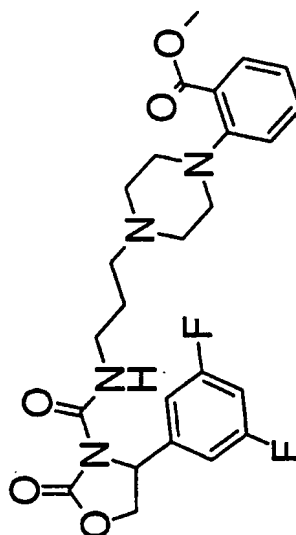
Compound 6



Compound 8

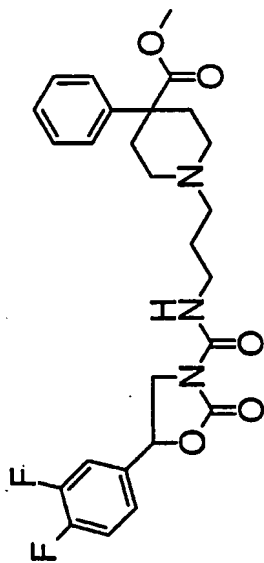


Compound 5

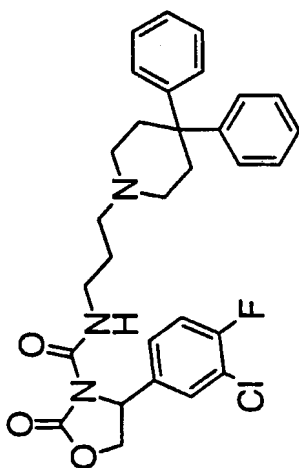


Compound 7

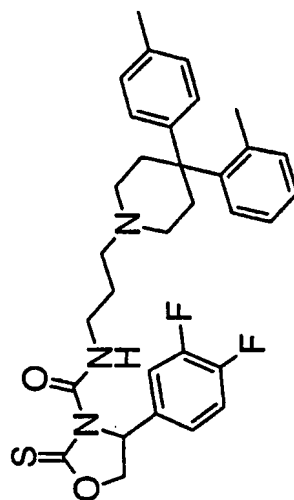
FIG. 1C



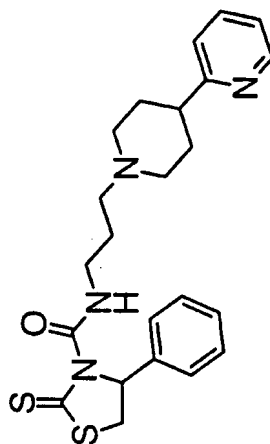
Compound 9



Compound 10



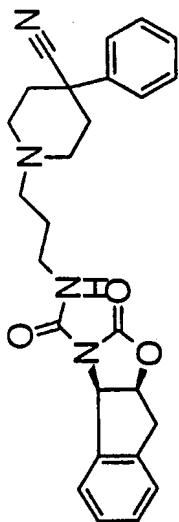
Compound 11



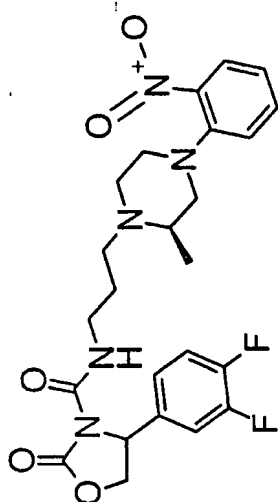
Compound 12

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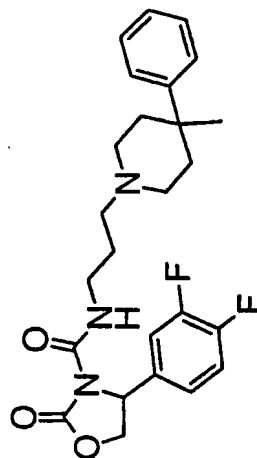
FIG. 1D



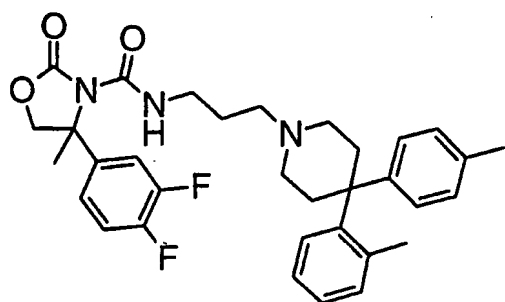
Compound 13



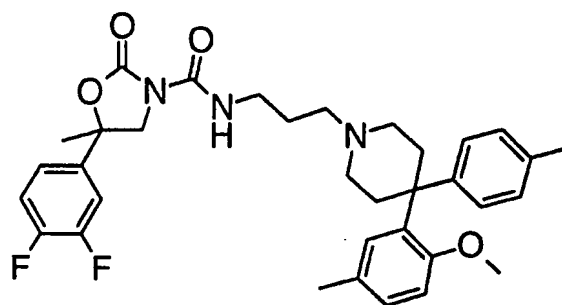
Compound 14



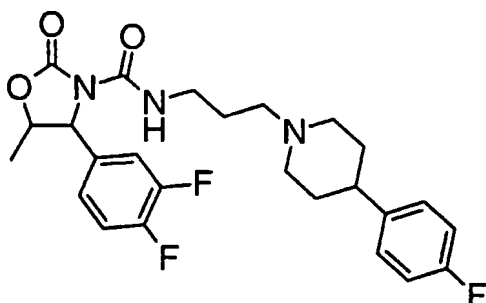
Compound 15



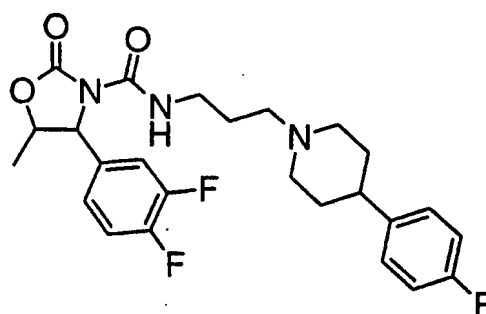
Compound 16



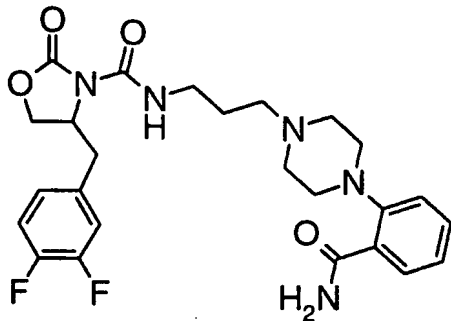
Compound 17



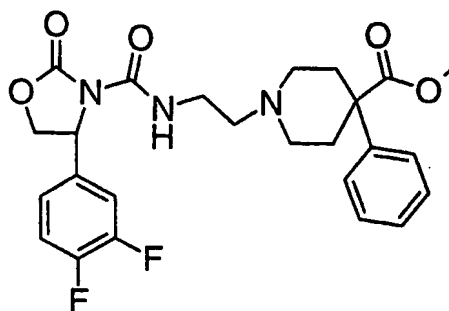
Compound 18



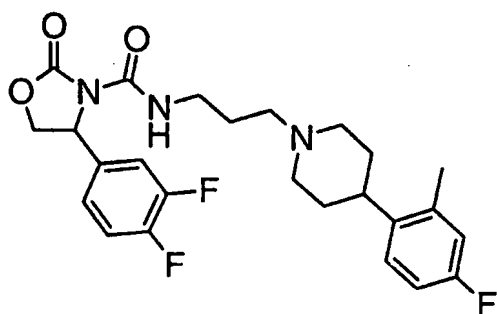
Compound 19



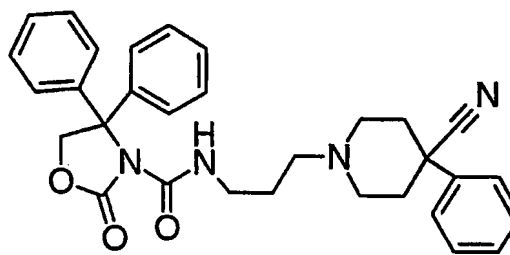
Compound 20



Compound 21



Compound 22

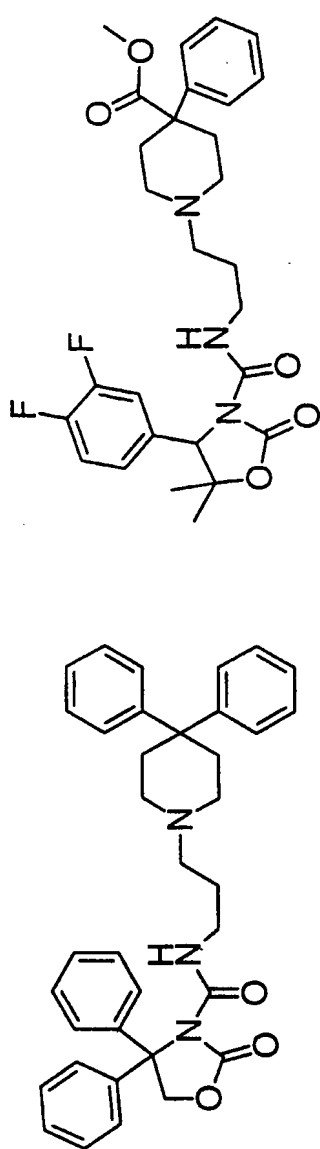


Compound 23

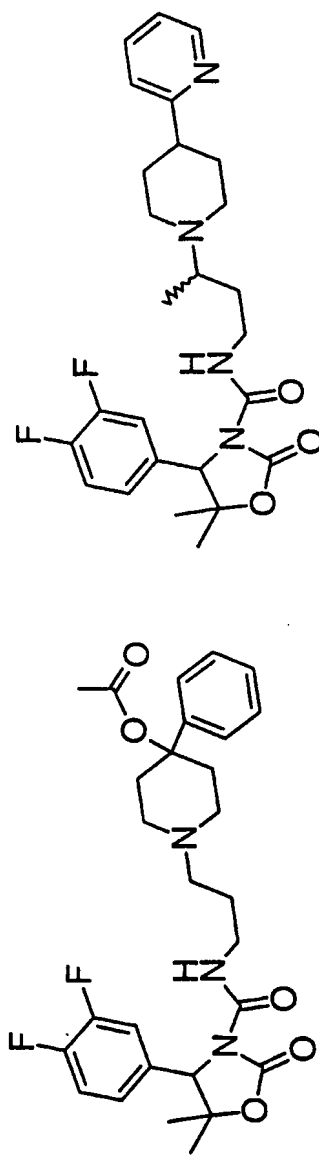
FIG. 1E

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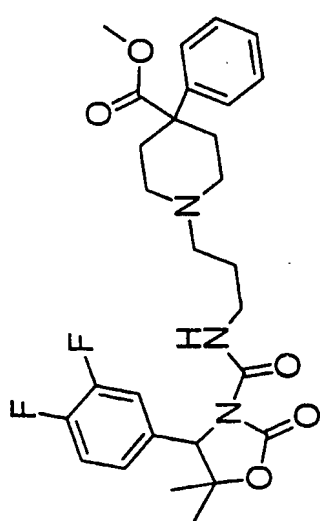
FIG. 1F



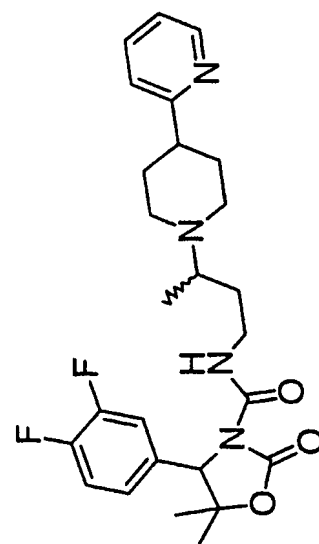
Compound 24



Compound 26

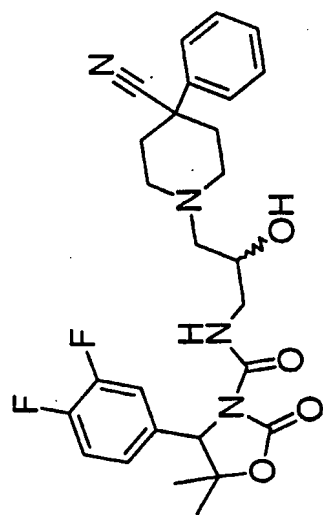


Compound 25

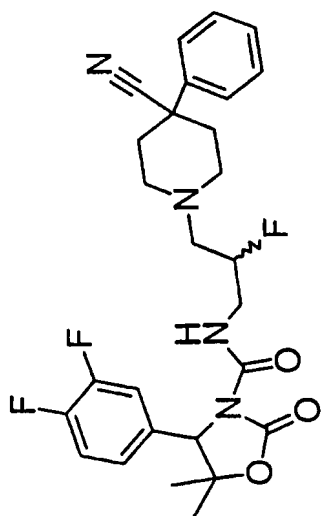


Compound 27

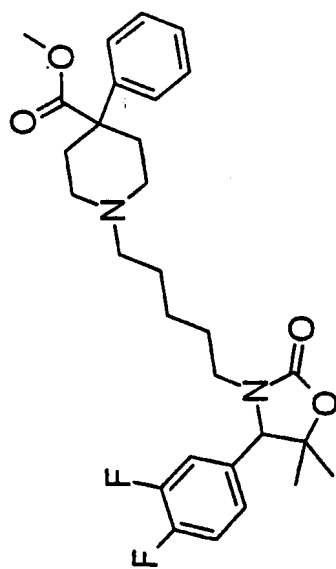
FIG. 1G



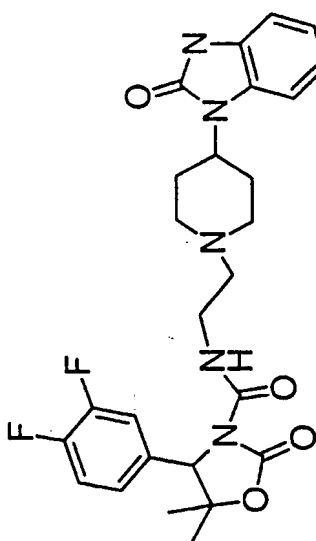
Compound 28



Compound 29

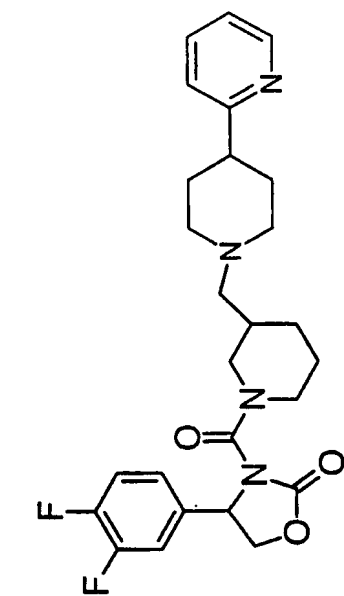


Compound 30

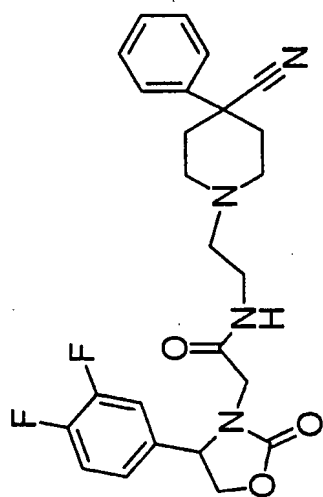


Compound 31

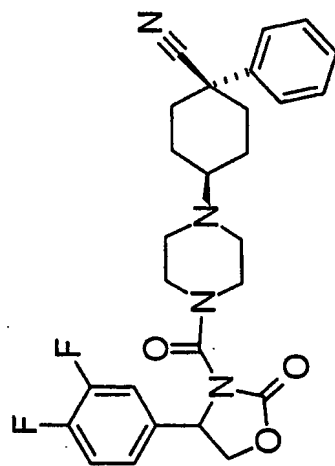
FIG. 1H



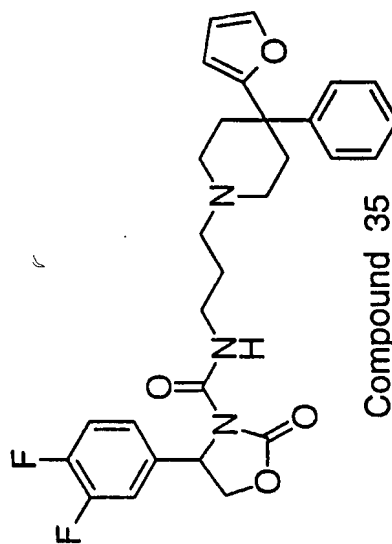
Compound 32



Compound 33



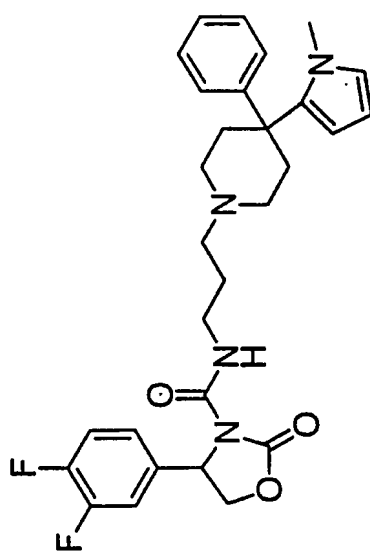
Compound 34



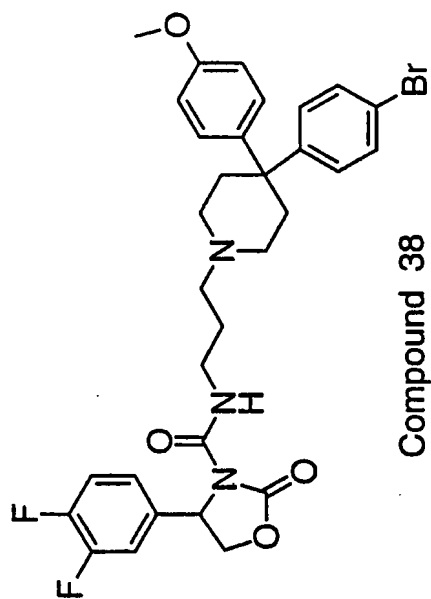
Compound 35

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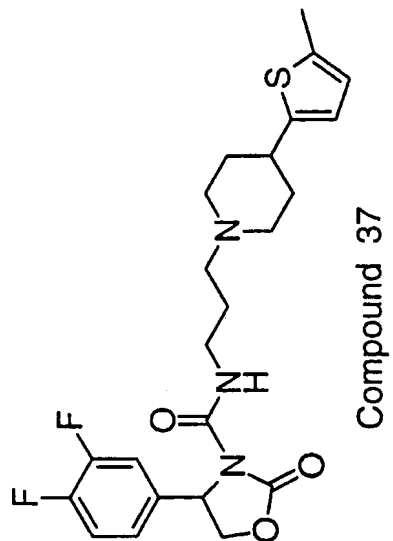
FIG. 11



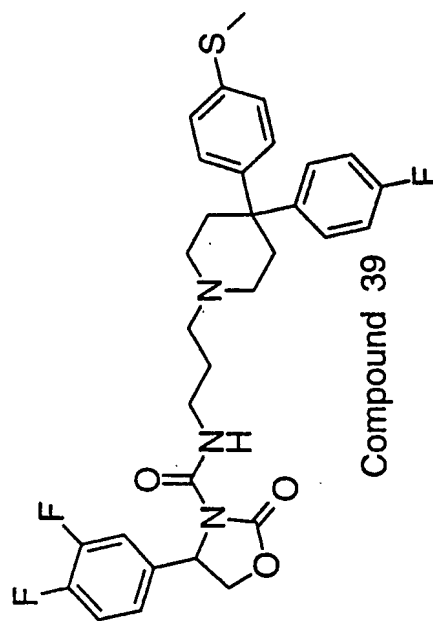
Compound 36



Compound 38



Compound 37



Compound 39

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FIG. 1J

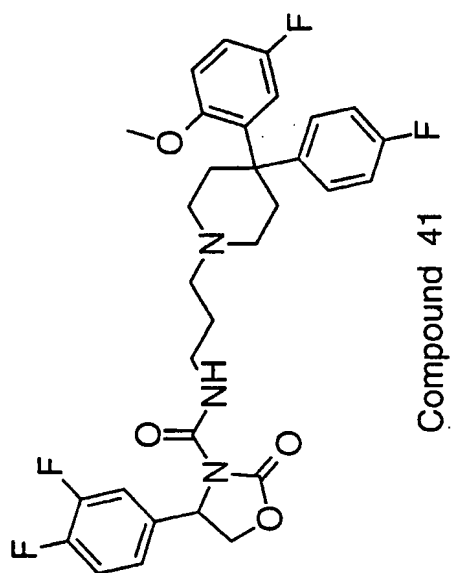
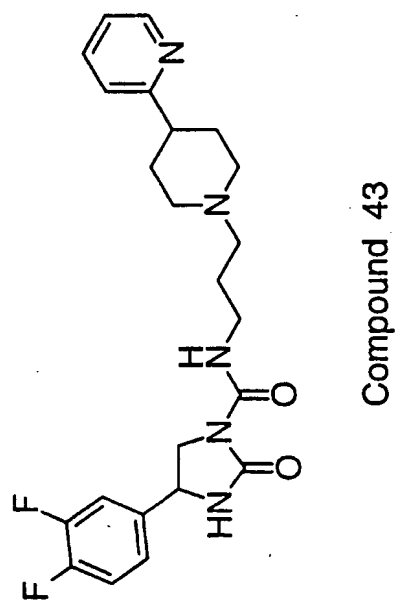
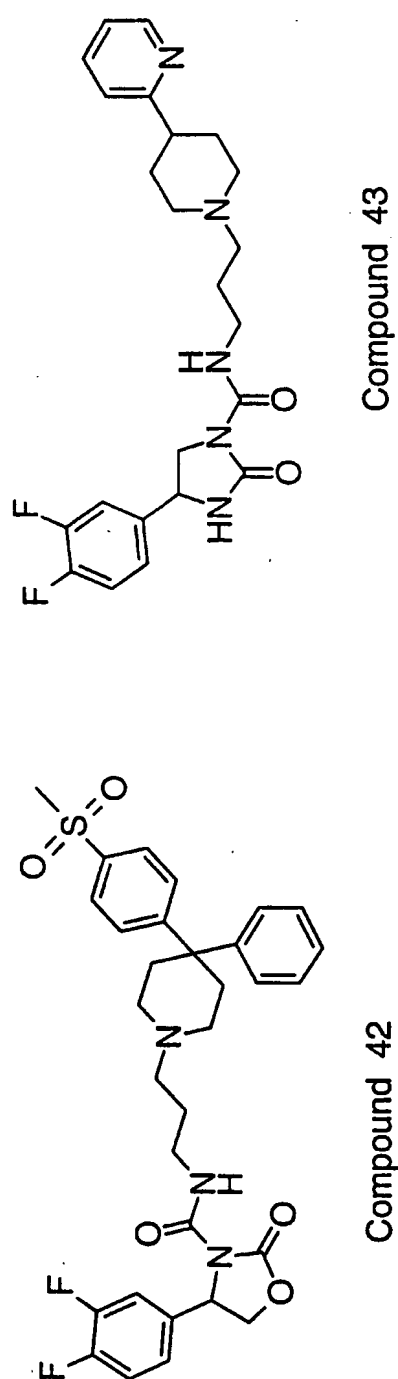
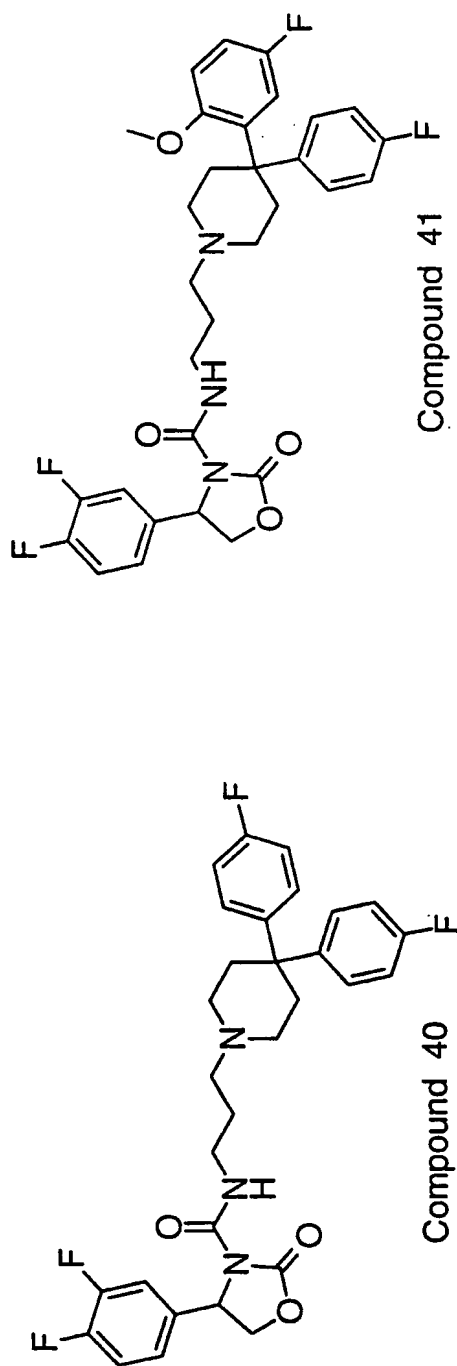
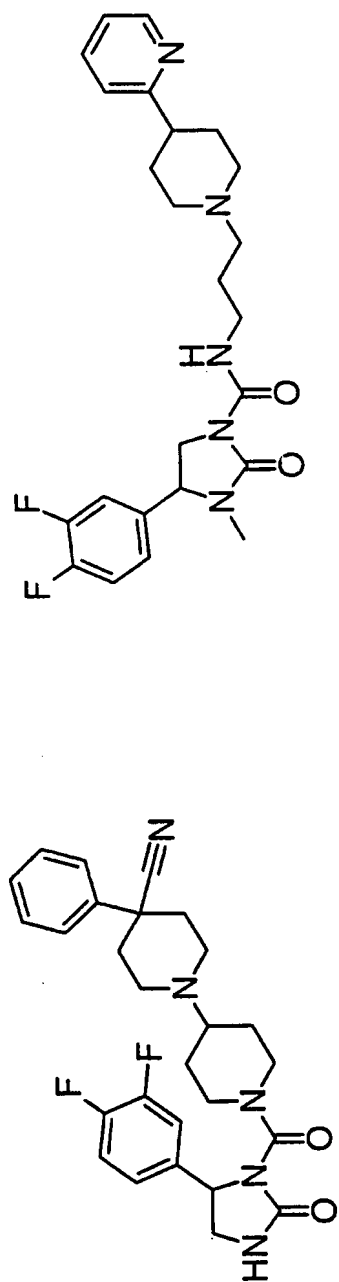
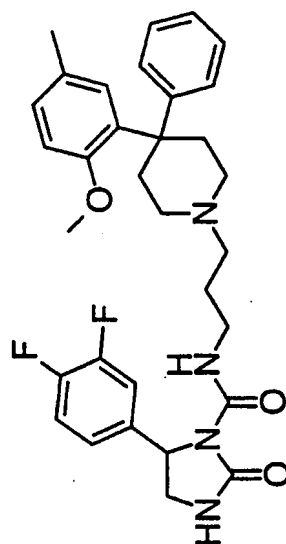


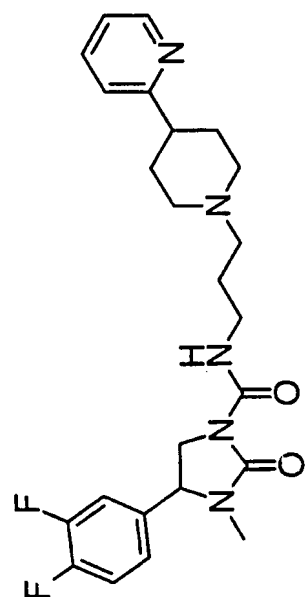
FIG. 1K



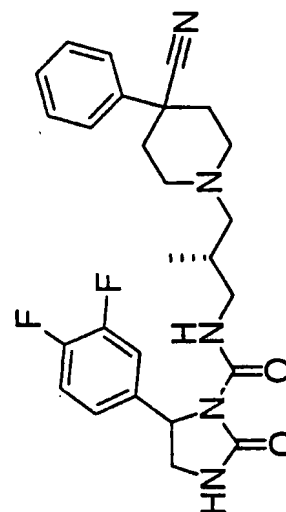
Compound 44



Compound 46

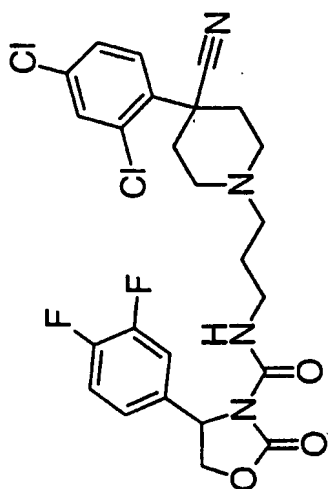


Compound 45

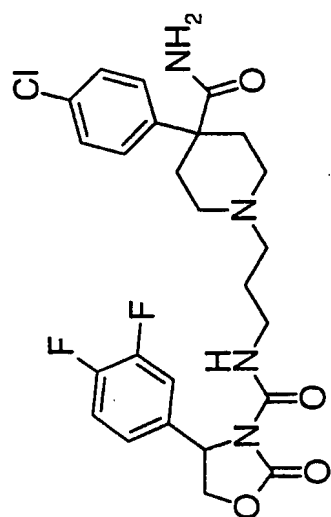


Compound 47

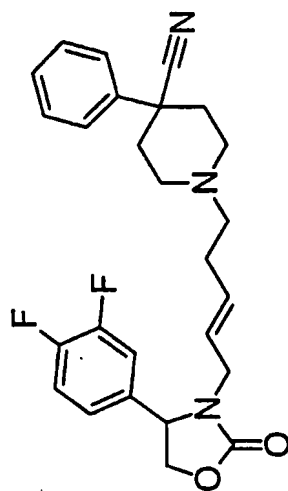
FIG. 1L



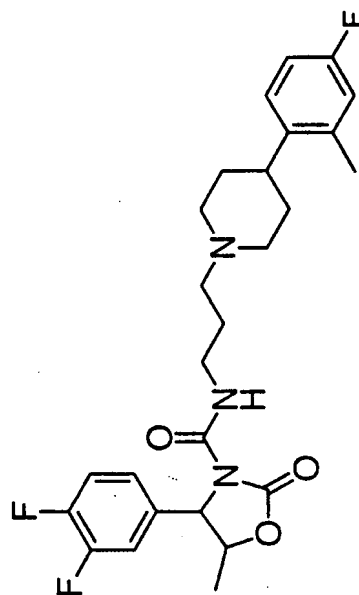
Compound 48



Compound 49



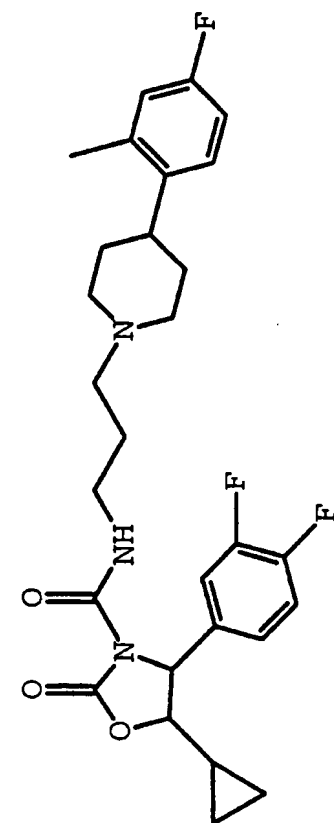
Compound 50



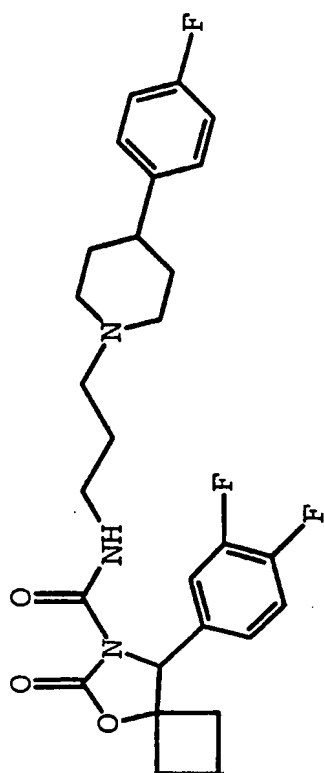
Compound 51

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FIG. 1M 13/13



Compound 53



Compound 52

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/12668

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/96, 369, 370; 546/187, 209, 210; 548/147, 216
514/230.8, 252, 331, 365, 374

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,882,431 A (ISHIMITSU et al.) 21 November 1989, columns 5-10, compounds 1, 3-5, 9, 10, 14, 17, 20, 23.	1-22, 28, 64
A	US 4,089,861 A (KYBURZ, E.) 16 May 1978, column 8, lines 12-13.	1-22, 28, 64
X	US 4,377,578 A (VANDENBERK et al.) 22 March 1983, columns 21-22, first 15 compounds and last 3, columns 23-24 Table Ia, columns 25-28, Table Id, Ic, columns 29-30, Table Ie.	1-11, 13, 18, 22-30
A	US 4,410,540 A (SCHNETTLER et al.) 18 October 1983, claim 1, columns 11-12.	1-64



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

06 AUGUST 1998

Date of mailing of the international search report

03 SEP 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Washington, D.C. 20231

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Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12668

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,334,098 A (WRIGHT et al.) 01 August 1967. See claim 1, column 6 and Example 1, column 3, examples 5-7, column 4, examples 12-14, 16-19, columns 5 and 6.	1-11, 13-15, 22, 28, 64
Y, P	US 5,698,573 A (CARLING et al.) 16 December 1997, column 5, lines 35-63.	62
X	US 5,202,345 A (MATSUMURA et al.) 13 April 1993. See column 1, line 35 to column 2, line 28 and formula 1c, see columns 7-14, Table 1, Nos. 14-17, 25-33, and columns 33, Table 11, Nos. 59-65.	1-10, 22-30
X	US 4,804,657 A (KOGURE et al.) 14 February 1989, see claims 1-6.	1-11, 13, 15, 19-31, 64
A	JOSHI, K et al. Fluorine Containing Bioactive Heterocycles, Part II. Synthesis of Some New Fluorine Containing Arylglyoxals, Their Hydrates and 1,5-Disubstituted Hydantoins. J. Heterocyclic Chem. 1981, Vol. 18, pages 1651-1653.	1-64
A	EP 0 599 749 A1 (RHONE POULENC) 01 June 1994, see abstract.	63

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/12668

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/12668

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6): C07D 263/20, 277/14, 403/06, 411/12, 413/12,
A61K 31/415, 31/42, 31/425, 31/445, 31/495, 31/505

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/230.8, 252, 269, 316, 331, 365, 374;
544/96, 369, 370; 546/187, 209, 210; 548/147, 216

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

- I. Claims 1-5, 22, 49-52, 64 (parts) to oxazines (q is 2).
- II. Claims 1-5, 22, 49-52, 64 (parts) to pyrimidines (q is 2).
- III. Claims 1-5, 22, 49-52, 63, 64 (parts) to piperazines.
- IV. Claims 1-3, 49-52, 63 (parts) 57-62 to piperidines.
- V. Claims 1-5, 22-31, 49-53, 63 (parts) to thiazoles not above provided.
- VI. Claims 1-5, 22-31, 49-52, 63 (parts) to oxazoles not above provided.
- VII. Claims 1-5, 22-31, 49-52, 63 (parts) to imidazolones not above provided.
- VIII. Claims 1-5, 22, 31, 49-52, 63 (parts) to heteroaryls not above provided.
- IX. Claims 32-48, 53-6 to multiple uses of I-VIII.

There is no common core/special technical feature required by PCT Rule 13.2. Lack of unity within claims is permitted, PCT Rule 13.3. ("Heteroaryl" cannot be completely searched in PTO files.)